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# THE EFFECT OF GROWTH HORMONE ON NITROGEN BALANCE AT VARIOUS LEVELS OF INTAKE IN BURNED PATIENTS

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THE MOST RECENT WORK with growth hormone has indicated that the monkey or human preparation has the most consistent anabolic effect in human beings. However, earlier studies (9, 11) had suggested that bovine growth hormone would cause a beneficial effect on the nitrogen balances of burned patients if it were given the proper substrate.

The impression had been gained from the previous studies that during the catabolic phase, administration of growth hormone was associated with an increased catabolic effect regardless of the level of nitrogen intake. During the anabolic phase, growth hormone seemed to enhance the storage of nitrogen when the nitrogen intake was 10 grams or more per square meter of body surface per day.

The present study was undertaken to elucidate the relationship between the level of intake and the effect of growth hormone on the burned patient during the catabolic and anabolic phases. Two methods of administration, intramuscular and intravenous, were evaluated, since the possibility existed that the growth hormone might be inactivated by tissue antibodies. In addition, the metabolic response was observed when desoxycorticosterone acetate was given simultaneously with growth hormone.

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## METHODS

The 6 patients were men between the ages of 20 and 25 years with comparable areas of burn. The burn index of the patients was calculated, as previously (14), as the area of third degree plus one-quarter of the area of second degree burn and ranged from 10 to 15. It has been observed that burns of this magnitude are associated with large losses of nitrogen, yet the patients can tolerate high levels of oral intake. Furthermore, differences in the surgical management of individual patients that are necessitated when there are large variations in the extent of the third degree area were eliminated.

The 24 days of the study of the catabolic phase began on postburn day 10 or 14, and

TABLE I.—EXPERIMENTAL PLAN, CATABOLIC AND ANABOLIC PHASES

| Patient No. | Surface area, m.² | Method of admin. | Level of intake | Periods | | |
|---|---|---|---|---|---|---|
| | | | | Control | GH Gm N/M² | Control |
| 51 | 1.7 | IM | High | 17.3 | 17.3 | 17.3 |
| | | | Low | 6 1 | 6.1 | 6.1 |
| 52 | 1.8 | IM | Low | 6.1 | 6.1 | 6.1 |
| | | | High | 17.3 | 17.3 | 17.3 |
| 54 | 1.7 | IV | High | 17.3 | 17.3 | 17.3 |
| | | | Low | 6.1 | 6.1 | 6.1 |
| 55 | 1.9 | IV | Low | 6.1 | 6.1 | 6.1 |
| | | | High | 17.3 | 17.3 | 17.3 |
| 50 | 2.0 | IM | | 9.9 | 9.9 | 9.9 |
| | | | | 9.9 | 9.9 | 9.9 |
| 53 | 2.0 | IM (DOCA) | | 9.9 | 9.9 | 9.9 |
| | | | | 9.9 | 9.9 | 9.9 |

the 24 days of the anabolic phase began on postburn day 59 or 60. During each phase, there were six 4 day periods with a 2 day interval after the third period. During this interval in the catabolic phase, 3 of the 6 patients were grafted, and all patients who required transfusions received them. No surgical procedures requiring anesthesia were performed nor transfusions given during the study periods. Two hundred milligrams of growth hormone[1] were administered daily, 50 milligrams every 6 hours, during 2 periods of each phase of the investigation. Each growth hormone period was preceded and was succeeded by a control period.

At the beginning of each study period of the catabolic phase, the patients were taken to the operating room, the wounds were washed and debrided without anesthesia and were dressed with vaseline gauze and occlusive dressings. Grafting was completed before the beginning of the study of the anabolic phase. No surgical complications were encountered in any of the patients in this study.

The total intake of each patient was determined by his normal body surface area in square meters. Subsequent references to nitrogen, potassium, and sodium intake are per square meter of body surface. Three levels of nitrogen intake per square meter were selected. By analysis they were: 6.1 grams, to determine whether growth hormone aggravates the existing catabolism when a low intake is given; 17.3 grams, to determine whether on a high intake increased storage takes place when growth hormone is given; and 9.9 grams, to confirm the results of the earlier study which indicated that this was the minimum amount necessary to elicit a response from growth hormone administration in terms of nitrogen utilization during the anabolic phase. The total calories were constant at 2,500 per square meter for all levels of nitrogen intake. No attempt was made to keep constant either the carbohydrate or fat for all levels of nitrogen.

The metabolic techniques of this institution have been described in detail (12). Liquid diets were prepared in the metabolic kitchen and consisted of dried whole milk, eggs, and dextri-maltose in varying proportions. Aliquots were analyzed periodically for nitrogen, potassium, and sodium. When the intake was incomplete, the unconsumed portion was analyzed.

Daily collections of urine, exudate, feces, and emesis were analyzed, and daily balances of nitrogen, potassium, and sodium were calculated. The dressings were removed in the operating room every fourth day, and the exudate content was allotted to the output of each day of that period. The feces were separated into 4 day specimens by carmine given the first day of each period. Blood samples were drawn on the morning of the first day of each particular period.

The urine was pooled to coincide with the study periods for steroid analyses. Urinary 17-ketosteroids were determined by acid hydrolysis, ether extraction, and color development with an aqueous alcohol Zimmerman method. Colorimetry was performed after extraction of Zimmerman color by the amyl acetate method of Masuda and Thuline. Urinary 11-oxycorticoids were

[1]On assay, the growth hormone used in this study was found to contain less than 5.0 U.S.P. units of ACTH per 100 milligrams. This lot was different from the one which was utilized in a previous study and which showed no ACTH contamination.

determined by glucuronidase hydrolysis, chloroform extraction, and measurement as Porter-Silber chromogen.

It has been shown that the metabolic response to trauma is altered with the passage of time. Since the purpose of the study was to measure the response to growth hormone by observing the changes in the balances when different levels of nitrogen were given, it was important to minimize the effect of time. To accomplish this, a cross-over experimental design was used. One patient was given the high nitrogen intake—17.3 grams—for the first 3 periods and the low nitrogen intake—6.1 grams—for the last 3 periods of each phase (Table I). The levels of intake were reversed for the second patient who was given the low level first and the high level last. The growth hormone was administered intramuscularly to patients 51 and 52, with very little discomfort at the sites of injection, and intravenously to patients 54 and 55. Fifty milligrams were infused over a 2 hour period every 6 hours in 250 milliliters of 5 per cent glucose in water. The same amount of 5 per cent glucose in water was infused during the control periods.

During the 2 day interval that followed the third study period, the 2 patients to whom the growth hormone was administered intramuscularly continued to receive their first level of intake. The pair who received the growth hormone intravenously were started on their second level of intake during this interval.

Patients 50 and 53 were given 9.9 grams of nitrogen throughout both phases of the study, and the growth hormone was administered intramuscularly. Patient 50 was given only the growth hormone and patient 53 received 2.5 milligrams of desoxycorticosterone acetate per day in addition to the growth hormone.

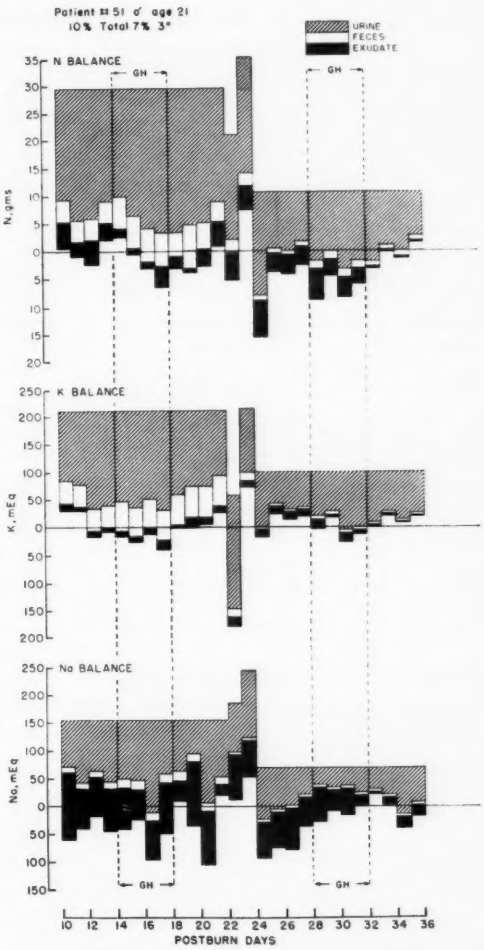


FIG. 1. Nitrogen, sodium, and potassium balances of the catabolic phase of Patient 51 who received the growth hormone intramuscularly. The intake is charted from the zero line up and the output charted from the intake line down. The shaded areas below the zero line indicate negative balance, and the clear areas above the zero line indicate positive balance.

## RESULTS

The data in Figures 1 through 12 are shown as total intake and balance and have been converted to intake and balance per square meter of body surface for the statistical analyses. The balances of the 2 day interval were not included in the analysis of the data.

*Changes of the cumulative balances during the growth hormone and control periods* (Table II). Catabolic phase.—The nitrogen balances of the 3 pairs of patients became more negative during the growth hormone periods. The balances of the succeeding control pe-

TABLE II.—CUMULATIVE INTAKE AND BALANCES PER SQUARE METER

| Patient No. | Nitrogen | | | Potassium | | | Sodium | | |
|---|---|---|---|---|---|---|---|---|---|
| | Intake grams | Control period, grams | GH period, grams | Control period, grams | Intake mEq. | Control period, mEq. | GH period, mEq. | Control period, mEq. | Intake, mEq. | Control period, mEq. | GH period, mEq. | Control period, mEq. |
| CATABOLIC PHASE | | | | | | | | | | | | |
| 51 | 17.3 | − 0.4 | − 4.9 | − 5.4 | 124 | + 23 | − 53 | +20 | 91 | − 94 | −124 | − 63 |
| (IM) | 6.1 | −15.8 | −16.8 | − 2.2 | 58 | + 22 | − 15 | +31 | 40 | −166 | − 32 | − 20 |
| 52 | 6.1 | −12.9 | −14.7 | − 7.3 | 58 | + 47 | − 34 | + 6 | 40 | −243 | −121 | −127 |
| (IM) | 17.3 | + 4.1 | − 0.1 | + 4.3 | 124 | + 2 | − 21 | −19 | 91 | −195 | − 26 | −138 |
| 54 | 17.3 | + 1.3 | −12.4 | −17.1 | 124 | +110 | − 64 | −37 | 91 | − 83 | −122 | − 59 |
| (IV) | 6.1 | −10.9 | −16.6 | −13.7 | 58 | − 16 | − 59 | + 7 | 40 | − 88 | + 15 | + 21 |
| 55 | 6.1 | −26.2 | −35.8 | −34.9 | 58 | + 20 | −124 | +33 | 40 | −318 | −190 | −236 |
| (IV) | 17.3 | + 9.8 | −14.8 | − 6.3 | 124 | + 21 | − 50 | −27 | 91 | +236 | − 29 | + 18 |
| 50 | 9.9 | − 8.7 | −13.7 | − 6.9 | 84 | + 28 | − 47 | −12 | 57 | − 78* | − 99* | + 40* |
| (IM) | 9.9 | − 2.9 | − 6.5 | + 0.9 | 84 | − 28 | − 35 | +24 | 57 | + 36* | + 40* | + 33* |
| 53 | 9.9 | −15.2 | −22.8 | −11.6 | 84 | − 20 | − 96 | −31 | 57 | −161* | + 74* | +105* |
| (DOCA) | 9.9 | + 0.9 | − 4.7 | − 3.4 | 84 | − 11 | − 23 | −80 | 57 | +151* | +147* | + 73* |
| ANABOLIC PHASE | | | | | | | | | | | | |
| 51 | 17.3 | +16.9 | +12.0 | +12.3 | 124 | + 69 | + 81 | +23 | 91 | − 46 | −106 | − 91 |
| (IM) | 6.1 | − 0.7 | − 1.0 | + 1.5 | 58 | + 40 | + 26 | +40 | 40 | − 70 | − 13 | −107 |
| 52 | 6.1 | − 3.6 | − 0.7 | − 3.0 | 58 | + 49 | − 9 | −23 | 40 | −119 | − 82 | − 64 |
| (IM) | 17.3 | +22.5 | +10.9 | + 5.6 | 124 | − 3 | + 32 | +53 | 91 | − 64 | + 55 | − 8 |
| 54 | 17.3 | +22.8 | +15.4 | +16.7 | 124 | + 87 | − 40 | +40 | 91 | −120 | − 64 | − 43 |
| (IV) | 6.1 | + 2.7 | − 0.7 | − 1.0 | 58 | + 62 | + 45 | +60 | 40 | −110 | − 73 | − 43 |
| 55 | 6.1 | − 5.6 | + 3.3 | + 7.5 | 58 | + 59 | + 85 | +54 | 40 | −124 | + 26 | − 29 |
| (IV) | 17.3 | +28.6 | + 9.6 | +20.8 | 124 | + 71 | + 83 | +93 | 91 | +121 | + 94 | + 25 |
| 50 | 9.9 | + 8.0 | + 7.3 | + 7.8 | 84 | + 62 | + 22 | + 8 | 57 | − 8 | − 3 | − 11 |
| (IM) | 9.9 | +13.7 | +14.5 | +10.7 | 84 | + 32 | + 53 | +23 | 57 | − 27 | + 21 | − 30 |
| 53 | 9.9 | +11.7 | +11.3 | + 4.6 | 84 | + 84 | + 67 | +23 | 57 | − 42 | + 47 | − 30 |
| (DOCA) | 9.9 | +13.3 | +16.2 | +12.5 | 84 | + 35 | + 69 | +12 | 57 | + 19 | + 66 | + 1 |

*Exudate sodium not included.

riod became less negative except after the first growth hormone period of patients 51 and 54.

The 3 pairs of patients also showed greater losses of potassium during the growth hormone periods. In the following control periods, the balances all became less negative or positive, with the exception of the last control period of patient 53.

In patients 51 and 52, the growth hormone administration was associated with a greater retention of sodium except during the first growth hormone period of patient 51. During the growth hormone periods of patients 54 and 55, there was a retention of sodium on the low intake and a loss of sodium on the high intake. In the first growth hormone period of patient 53, there was sodium retention; but there was only a slight change in the sodium balances during the other growth hormone periods of patient 53 and both periods of patient 50. The sodium balances of these patients were calculated from intake minus urinary sodium. None of the patients had a definite pattern in the changes of the balances of the succeeding control periods.

Anabolic phase.—The nitrogen balances of patient 51 became less positive during the growth hormone periods, whereas those of patient 52 became less negative during the first period or did not change appreciably during the second growth hormone period. In patients 54 and 55, the balances all became less positive except for the first growth hormone period of patient 55. The only change in the balances of patients 50 and 53 was an increased storage of nitrogen in the last growth hormone period of patient 53. The changes in the direction of the balances of all the succeeding control periods were inconsistent.

There was no consistent change in the potassium balances of any of the patients

TABLE III.—SUMMARY OF ANALYSIS OF VARIANCE FOR PATIENTS 51 AND 52 (IM)

| | *Catabolic phase* | | | *Anabolic phase* |
|---|---|---|---|---|
| *Source* | *N* | *K* | *Na* | *N* |
| Control periods vs. GH period..... | 4.20* | 10.82† | | |
| Control period vs. control period.. | | | 7.53† | |
| Level effect..... | 27.32‡ | | | 33.10‡ |

*Significant at 0.05 level.
†Significant at 0.01 level.
‡Significant at 0.001 level.

TABLE IV.—SUMMARY OF ANALYSIS OF VARIANCE FOR PATIENTS 54 AND 55 (IV)

| | *Catabolic phase* | | | *Anabolic phase* | |
|---|---|---|---|---|---|
| *Source* | *N* | *K* | *Na* | *N* | *Na* |
| Patient or order.. | 5.48* | | 17.76‡ | | 10.99† |
| Control periods vs. GH period..... | 3.40 | 10.57† | | | |
| Level effect..... | 17.73‡ | | 42.96‡ | 45.00‡ | 4.60* |
| Level—order IA.. | 6.38* | | 55.73‡ | | 4.65* |
| Level—period (Control vs. GH) | | 5.33* | | | |

*Significant at 0.05 level.
†Significant at 0.01 level.
‡Significant at 0.001 level.

TABLE V.—SUMMARY OF ANALYSIS OF VARIANCE FOR PATIENTS 50 AND 53

| | *Catabolic phase* | | *Anabolic phase* | |
|---|---|---|---|---|
| *Source* | *N* | *Na* | *N* | *Na* |
| Patient 50 | | | | |
| Control vs. GH..... | 4.10 | | | |
| Time..... | 6.18* | 6.70* | 5.48* | |
| Patient 53 | | | | |
| Control vs. GH-DOCA.... | 4.26 | 8.30† | | 4.37 |
| Control vs. control..... | | 25.47‡ | | |
| Time..... | 23.63‡ | 20.06‡ | 3.96 | |
| Time—Period IA..... | | 9.47† | | |

*Significant at 0.05 level.
†Significant at 0.01 level.
‡Significant at 0.001 level.

TABLE VI.—SUMMARY OF ANALYSIS OF VARIANCE FOR PATIENTS 50 AND 53 (GH AND GH-DOCA)

| | *Catabolic phase* | | *Anabolic phase* | |
|---|---|---|---|---|
| *Source* | *N* | *Na*§ | *N* | *Na* |
| GH vs. GH-DOCA (Patient 50 vs. Patient 53)..... | | 11.15† | | |
| Control periods vs. GH period | 8.72† | | | 4.72* |
| Control period vs. control period..... | | 8.83† | | |
| Time..... | 29.24‡ | 23.00‡ | 9.56† | |
| Time—period IA..... | | 10.42† | | |

*Significant at 0.05 level.
†Significant at 0.01 level.
‡Significant at 0.001 level.
§Balance calculated from intake minus urine.

during the growth hormone periods. In general, an increased storage of potassium occurred after the growth hormone periods of patients 51, 52, 54, and 55. In patient 50 and in patient 53 there was decreased storage.

In the 3 pairs of patients, the sodium balances became positive or less negative during the growth hormone periods, with the exception of the first period of patient 51 and the last period of patient 55. In the succeeding control periods, patients 50 and 53 lost some sodium and the other patients had no consistent pattern of change.

*Statistical analysis* (Tables III, IV, V, and VI). Catabolic phase.—In the summaries of the analyses of variance, only the F- values of those comparisons which were significant are indicated.

The comparison of greatest interest is that of the control versus growth hormone periods. The nitrogen and potassium balances of the control periods of patients 51, 52, 54, and 55 were significantly less negative than during the growth hormone period. There was a significant difference between the sodium balances of patients 50 and 53 (growth hormone versus growth hormone and desoxycorticosterone acetate, Table VI). During the growth hormone and desoxycorticosterone acetate periods of patient 53, the sodium balance was significantly more positive (Table V).

Anabolic phase.—The only significant effect noted between the control and growth hormone periods of the anabolic phase was that of the sodium balances of patients 50 and 53. The balances were significantly higher during the growth hormone and hormone plus desoxycorticosterone acetate periods of this pair (Table VI).

Balances without exudate.—Balances of nitrogen, sodium, and potassium were calculated for all of the patients, the exudate contribution being omitted, and the same statistical analysis was made as previously. This omission was made since losses from this source probably do not reflect the metabolic effect of growth hormone. The significant effects as earlier described in the section on total balances remained unchanged.

TABLE VII.—WEIGHT CHANGES OF PATIENTS

| Patient No. | Catabolic phase | | | | Anabolic phase | | | |
|---|---|---|---|---|---|---|---|---|
| | Control, kgm. | GH, kgm. | Control, kgm. | Total,* kgm. | Control, kgm. | GH, kgm. | Control, kgm. | Total,* kgm. |
| 51 | −1.6 | −1.3 | +0.7 | | +2.4 | +1.1 | 0 | |
| (IM) | −2.5 | −0.7 | 0 | −3.2 | +1.3 | +0.8 | +0.3 | +5.1 |
| 52 | −1.0 | −1.1 | +1.1 | | +0.8 | +0.2 | +0.1 | |
| (IM) | −0.7 | −2.5 | +0.5 | −0.9 | +1.0 | +2.3 | +0.3 | +5.2 |
| 54 | +0.5 | −0.3 | −0.2 | | +0.7 | −0.2 | −0.5 | |
| (IV) | +0.7 | +0.2 | +1.4 | +3.2 | +0.3 | −0.7 | +0.1 | −0.1 |
| 55 | 0 | −2.4 | −1.6 | | +0.8 | −1.0 | +0.7 | |
| (IV) | +1.7 | −3.3 | 0 | −2.2 | +2.4 | +0.1 | +0.4 | +3.9 |
| 50 | −0.2 | −2.4 | +0.6 | | +2.5 | +0.8 | +1.9 | |
| (IM) | 0 | −0.5 | +0.9 | +0.2 | +0.2 | +2.3 | +0.7 | +8.9 |
| 53 | −0.9 | −2.5 | −0.4 | | +1.6 | +2.3 | −0.4 | |
| (DOCA) | +1.2 | +0.6 | +1.2 | −3.4 | +1.8 | +3.1 | 0 | +9.1 |

*The difference in weight at the beginning and end of the study which includes the 2 day interval.

*Weight changes.* During the catabolic phase, there were periods when the individual patients gained weight (Table VII). With the exception of patient 51, there was a greater loss or smaller gain of weight during the growth hormone periods than during the preceding control periods. The loss of weight was statistically significant for patients 54, 55, 50, and 53 (Table VIII). In the following control periods, all of the patients either gained or had a smaller loss of weight than during the growth hormone periods.

In the anabolic phase, there was a decreased rate of gain or a loss of weight during most of the growth hormone periods except for patient 53. The weight changes were statistically significant for patients 54 and 55. In general, the rate of gain continued to diminish or there was a weight loss in the succeeding control periods except for patient 55.

*Urinary steroids* (Table IX). The levels of excretion of 17-ketosteroids were essentially within normal limits and showed no consistent changes during the catabolic and anabolic phases.

Catabolic phase.—In patients 54 and 55, the level of 11-oxycorticoid excretion was either elevated or at the upper limit of normal. There appeared to be a marked and distinct rise in the excretion of 11-oxycorticoids during the growth hormone periods. The exception was patient 53 who received desoxycorticosterone acetate in addition to growth hormone and who showed a fall in the excretion of 11-oxycorticoids during his first growth hormone period.

Anabolic phase.—The level of excretion of 11-oxycorticoids was, with few exceptions, within normal limits. Except for patient 53, a slight rise in urinary corticoid excretion was observed during the growth hormone periods.

Generally, the nitrogen balances correlated well with the change in the 11-oxycorticoids, that is, there was diminished nitrogen storage associated with the rise in 11-oxycorticoid excretion. Three normal subjects were also studied. These volunteer controls received growth hormone from the same lot as the patients. They showed a very slight rise in 11-oxycorticoid excretion during growth hormone therapy. This rise averaged 0.6 milligram per day and was similar to that observed in the patients during the anabolic phase.

*Temperature changes.* During the entire catabolic phase, all of the patients had a slight elevation of temperature ranging between 99 and 102 degrees F. The daily temperature elevations averaged 1 degree F. higher during the growth hormone periods but this difference was not significant. Patient 55 had a temperature of 103 degrees F. and above during the entire catabolic phase of his study. During the anabolic phase, the daily temperature elevations ranged between 99 and 101 degrees F. and were

slightly greater during the growth hormone periods.

*Pattern of plasma chemistries and hematology.* The pattern of plasma electrolyte concentrations was the same as that seen in other patients with burns of similar magnitude. There was moderate hyponatremia, moderate anemia, and the albumin values were at the lower limit of normal throughout the catabolic phase of the study. During the anabolic phase, all of these parameters were within normal limits during the control and growth hormone periods. The eosinophils did not fall significantly during the growth hormone periods.

## DISCUSSION

There is considerable experimental evidence that bovine growth hormone causes increased nitrogen storage in animals. In normal and fasting dogs, Bartlett found that with growth hormone there was an increase in the size of the nitrogen pool, an increase in the rate of protein synthesis, and a decrease in the rate of protein degradation. Russell concluded from her experiments with nephrectomized rats that the action of growth hormone is primarily to increase the rate of protein synthesis but not to decrease the rate of protein catabolism.

In human beings who have been given bovine growth hormone, however, the results are somewhat equivocal. Carballiera and associates showed that after the intravenous administration of growth hormone in an amino acid solution to normal men, there was a lowered plasma level and a diminished rate of excretion of amino acids. Crispell and Shorr and associates, however, found an inconsistent increase in the rate of protein synthesis and storage in normal human beings and in patients with endocrine disorders.

The observations made in patients after surgical trauma are somewhat sparse and contradictory. When Moore administered bovine growth hormone late in convalescence to several patients who had undergone operative procedures of moderate magnitude, he found no consistent protein-sparing effect. In burned patients, the findings which suggested an enhanced storage of protein were based on observations of nitrogen and mineral balances made late in the postburn course and were confirmed by the measurement of an increased rate of incorporation of sulfur-labelled methionine into the plasma proteins when growth hormone was given.

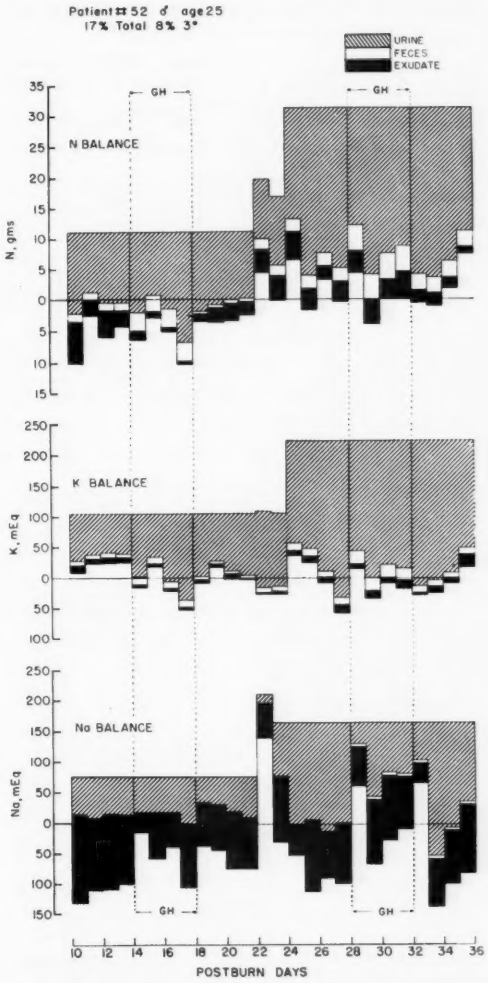


FIG. 2. Nitrogen, sodium, and potassium balances of the catabolic phase of Patient 52 who received the growth hormone intramuscularly. The method of charting for all figures is described in the legend of Figure 1.

TABLE VIII.—WEIGHT CHANGES, SUMMARY OF ANALYSIS OF VARIANCE

| *Source* | *Patients 51 and 52* | *Patients 54 and 55* | *Patients 50 and 53* |
|---|---|---|---|
| CATABOLIC PHASE | | | |
| Control periods vs. GH period . . . | 4.28 | 6.62* | 12.04† |
| Control period vs. control period. | 14.22* | | 14.15† |
| ANABOLIC PHASE | | | |
| Control periods vs. GH period . . . | | 9.01* | |
| Control period vs. control period. | 7.37* | 4.58 | |

*Significant at 0.05 level.
†Significant at 0.01 level.

TABLE IX.—URINARY STEROIDS

| *Patient No.* | *11-Oxycorticoids* | | | *17-Ketosteroids* | | |
|---|---|---|---|---|---|---|
| | *Control period, mgm./day* | *GH period, mgm./day* | *Control period, mgm./day* | *Control period, mgm./day* | *GH period, mgm./day* | *Control period, mgm./day* |
| CATABOLIC PHASE | | | | | | |
| 54 | 5.2 | 11.6 | 7.7 | 17.5 | 18.8 | 18.2 |
| | 7.2 | 9.0 | 7.7 | 14.8 | 23.0 | 20.4 |
| 55 | 12.0 | 29.0 | 9.0 | 21.9 | 10.8 | 6.4 |
| | 6.4 | 13.2 | 13.2 | 7.1 | 8.8 | 23.7 |
| 53 | 5.0 | 3.8 | 4.9 | 14.8 | 17.1 | 12.1 |
| | 3.9 | 4.0 | 6.1 | 14.2 | 13.5 | 17.8 |
| ANABOLIC PHASE | | | | | | |
| 51 | 3.7 | 4.1 | 5.1 | 7.6 | 7.5 | 9.6 |
| | 4.2 | 6.1 | 4.4 | 9.5 | 3.4 | 1.5 |
| 52 | 5.9 | 7.4 | 5.7 | 19.6 | 19.0 | 20.2 |
| | 9.8 | 11.0 | 8.5 | 22.0 | 14.1 | 12.4 |
| 54 | 4.6 | 7.4 | 5.3 | 14.1 | 18.8 | 16.3 |
| | 5.2 | 5.4 | 4.6 | 18.6 | 12.6 | 13.2 |
| 55 | 9.9 | 6.2 | 6.1 | 13.6 | 15.8 | 19.5 |
| | 7.2 | 9.4 | 5.8 | 17.8 | 21.5 | 18.4 |
| 50 | 4.6 | 5.9 | 6.1 | 14.9 | 18.6 | 15.7 |
| | 4.9 | 5.6 | 4.9 | 13.6 | 23.1 | 22.4 |
| 53 | 6.1 | 4.6 | 5.3 | 20.3 | 15.6 | 19.6 |
| | 6.0 | 4.2 | 5.6 | 16.4 | 12.0 | 15.7 |

Specimens of the catabolic phase of patients 50, 51, and 52 were lost.
Normal values, adult males: 11-oxycorticoids: 2.5–6.0 mgm. per day.
17-ketosteroids: 13.0–22.0 mgm. per day.

However, there have been no investigations made of the role of growth hormone at the height of the catabolic response to severe trauma.

*Effects of levels of intake and of route of administration upon the balances.* Nitrogen.—In the patient on the nitrogen intake of 6.1 grams during the catabolic phase, the intramuscular administration of growth hormone did not appreciably increase the existing catabolism as measured by the negative nitrogen balance (Table II). However, when it was given intravenously the losses increased. During the anabolic phase when the nitrogen level of 6.1 grams was given first, growth hormone seemed to enhance nitrogen utilization irrespective of the method of administration. But when it was given last, and previous storage had occurred with the high intake, intramuscular administration of growth hormone did not alter the nitrogen balance, and the intravenous administration decreased it slightly.

During the catabolic phase, there was an increased loss of nitrogen during the growth hormone periods with an intake of 9.9 grams. In the anabolic phase, there was nitrogen storage during all the periods, and the changes in balances were small during the growth hormone periods. The previous study had indicated that during the anabolic phase, if at least 10 grams of nitrogen were given with growth hormone, nitrogen retention would be enhanced.

On the nitrogen intake of 17.3 grams, the nitrogen balance became more negative during the catabolic phase and less positive during the anabolic phase, irrespective of the order of administration of the intake and the route of administration of the growth hormone. The increased nitrogen excretion during the growth hormone periods appears to indicate either an inability to utilize the high levels of nitrogen ingested or an increased mobilization and excretion of some of the nitrogen stored during the preceding control period. The present experiments do not differentiate the relative importance of these two possible mechanisms.

Potassium.—During the catabolic phase, the potassium balances became more negative during the periods of growth hormone administration. The magnitude of the changes were similar for all levels of intake with the intramuscular growth hormone. The greatest decrease in the balances was noted when the growth hormone was given intravenously. During the anabolic phase with the intramuscular administration of growth hormone, the potassium balances became more positive on the highest intake and more negative on the lowest level. The intermediate level and intravenous administration resulted in variable changes. This is

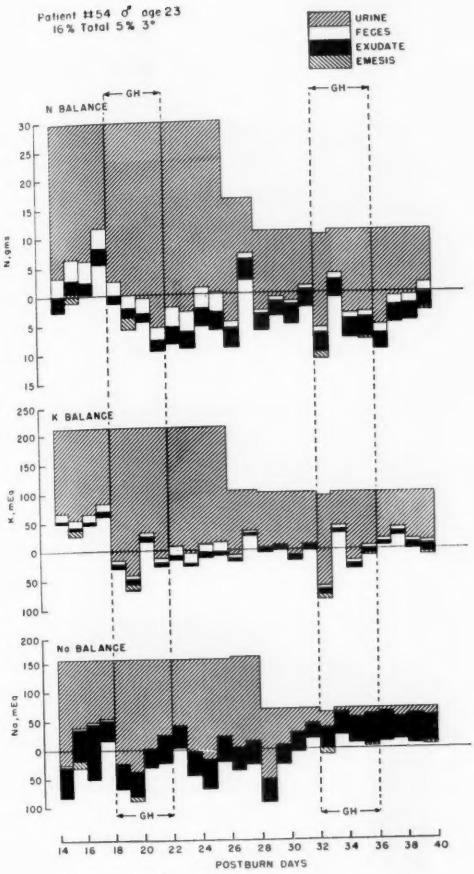


FIG. 3.

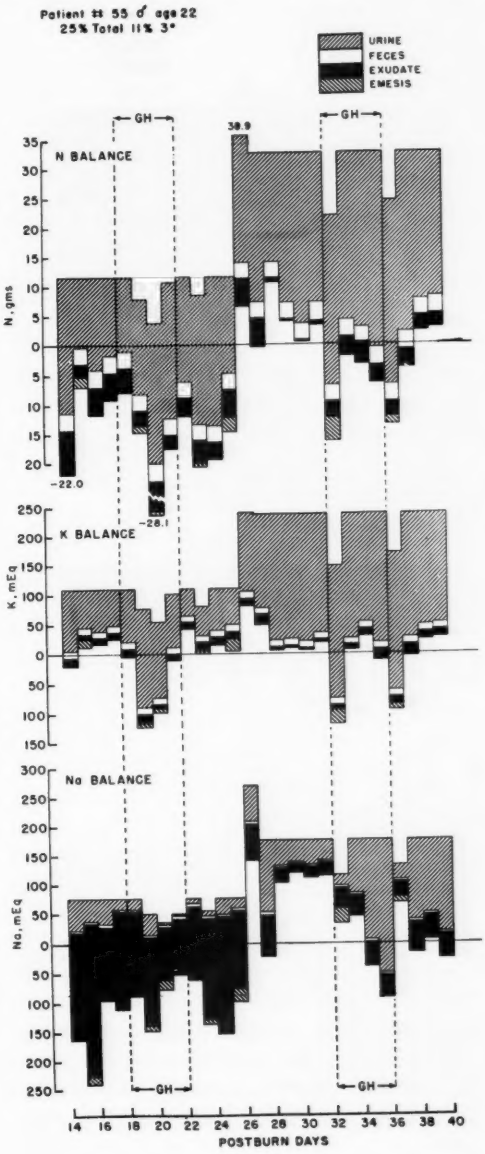


FIG. 4.

FIG. 3. Nitrogen, sodium, and potassium balances of the catabolic phase of Patient 54 who received the growth hormone intravenously.

FIG. 4. Nitrogen, sodium, and potassium balances of the catabolic phase of Patient 55 who received the growth hormone intravenously.

in keeping with the previous study (9) which suggested that there was a critical level of potassium intake roughly equivalent to the lowest level of this study, above which growth hormone administration will enhance storage.

Sodium.—During the catabolic phase, the sodium balances became less negative on the lowest intake during the growth hormone periods, irrespective of the route of administration. The changes in balance in the other two levels were inconsistent. During all but 2 growth hormone periods of the anabolic phase, the sodium balance became either less

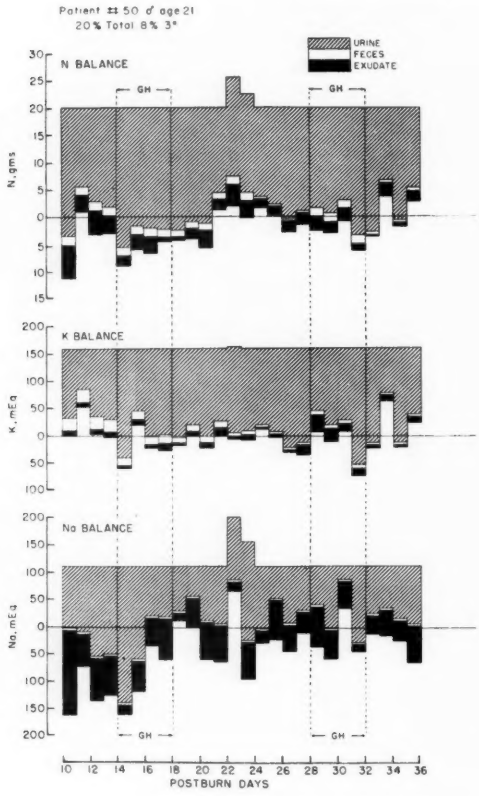


FIG. 5.

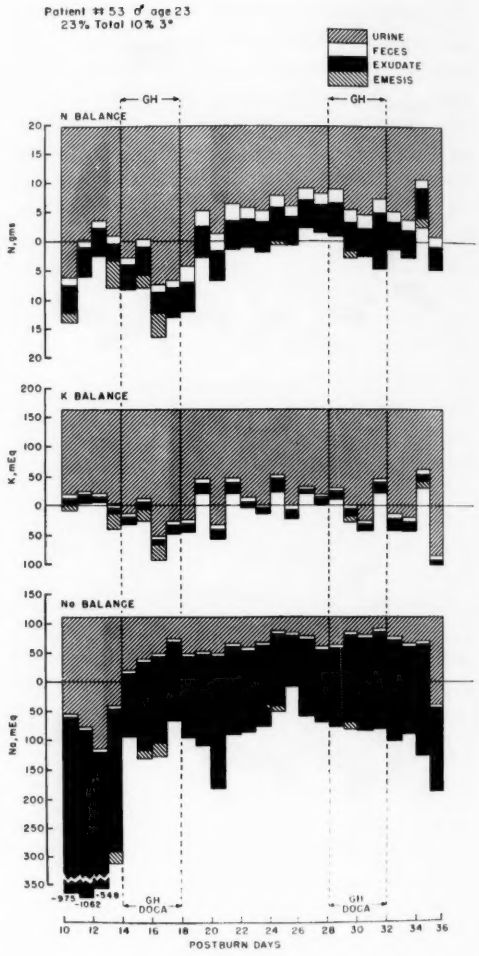


FIG. 6.

FIG. 5. Nitrogen, sodium, and potassium balances of the catabolic phase of Patient 50 who received the growth hormone intramuscularly.

FIG. 6. Nitrogen, sodium, and potassium balances of the catabolic phase of Patient 53 who received growth hormone intramuscularly. Desoxycorticosterone acetate was given in addition to the growth hormone.

negative or more positive, irrespective of the level of intake. The method of administration had little effect on the magnitude of the changes in the balances observed in this study.

Growth hormone did not prove beneficial during the catabolic phase on any level of intake given, a fact strongly suggested during the previous studies. During the anabolic phase, the magnitude of the changes in the positive nitrogen balances during growth hormone administration on either the predetermined level of 10 grams per square meter or the 6.1 grams per square meter intake was less than the change on the highest intake. This may be due to the composition of the diets: the nonprotein calories diminished as the nitrogen content of the intake increased. The lower levels of nitrogen intake furnished more exogenous energy than the highest intake and had a greater protein-sparing effect. What is normally considered an adequate intake may be inadequate when the subject's anabolic activity is greatly increased.

Gump and associates have recently re-

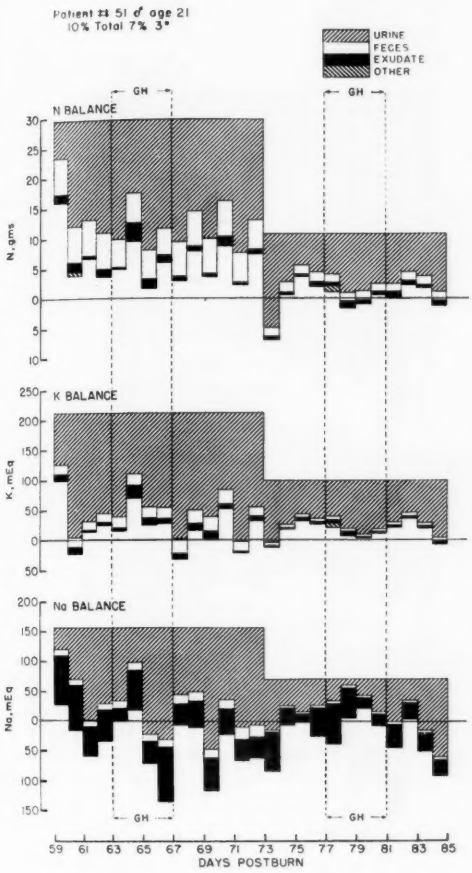


FIG. 7.

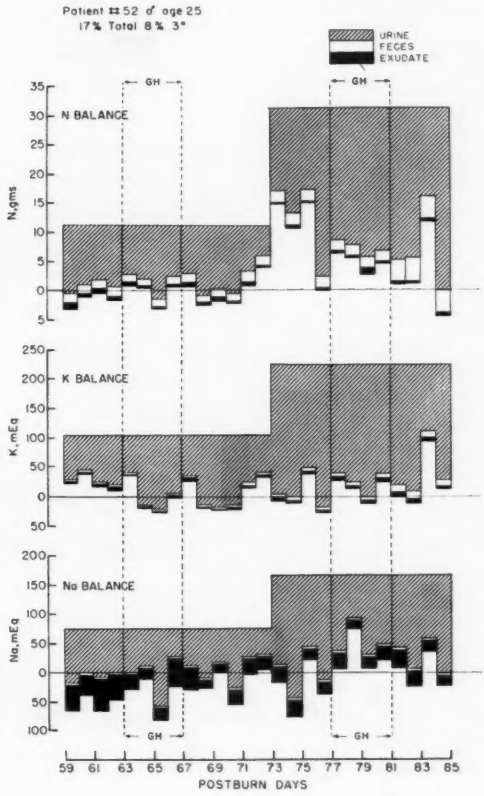


FIG. 8.

FIG. 7. Nitrogen, sodium, and potassium balances of the anabolic phase of Patient 51.

FIG. 8. Nitrogen, sodium, and potassium balances of the anabolic phase of Patient 52.

ported that without an adequate caloric intake weight losses in traumatized rats are accelerated by the administration of growth hormone to this species of experimental animal.

Bondy has shown that one of the first measurable responses to growth hormone in man is an elevation of blood ketone bodies which suggests that one of the mechanisms for the protein-sparing action of growth hormone is the mobilization of body fat as the primary source of energy. This is further supported by Greenbaum's observations in rats that the growth induced by growth hormone ceases when body fats are exhausted. The patients reported here undoubtedly had catabolized much of their available body fat by the time the studies began. This would suggest that there was insufficient endogenous fat to support any increased anabolism which the growth hormone might have stimulated and, therefore, that the dietary protein was utilized for energy and was excreted.

The rise in 11-oxycorticoid excretion during the growth hormone periods of the catabolic phase suggests that there was increased adrenal cortical activity associated with the increased excretion of nitrogen and potassium. It would seem unlikely that ACTH contamination could account for all of these changes, since the normal subjects had only

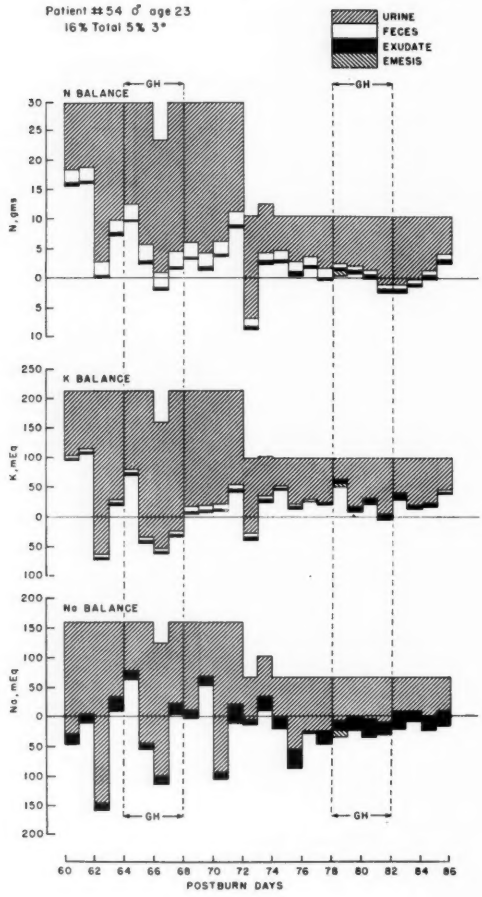


FIG. 9.

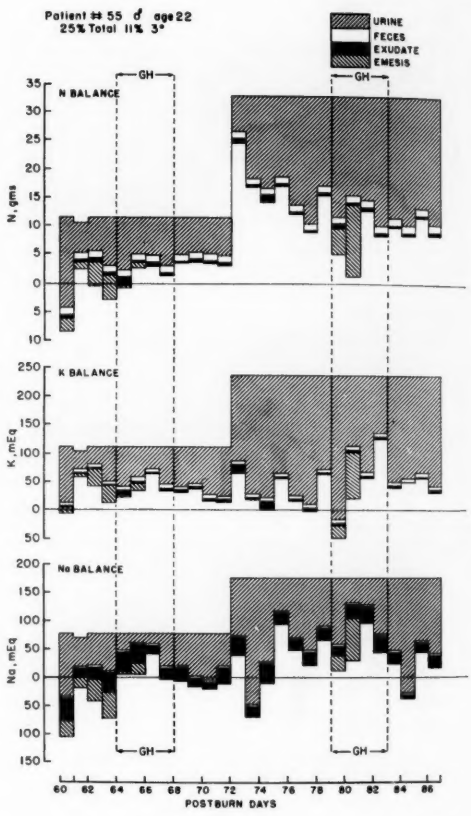


FIG. 10.

FIG. 9. Nitrogen, sodium, and potassium balances of the anabolic phase of Patient 54.
FIG. 10. Nitrogen, sodium, and potassium balances of the anabolic phase of Patient 55.

a minimal increase in the 11-oxycorticoid excretion.

*Effect of growth hormone administered with desoxycorticosterone acetate.* Desoxycorticosterone acetate characteristically causes a decrease in the urinary sodium and occasionally an increase in urinary potassium. Patient 53 who received a maintenance dose of desoxycorticosterone acetate and growth hormone exhibited this decrease in urinary sodium in the first hormone and steroid period of the catabolic phase. The sodium excretion remained at a low level until the final day of the last control period. That this is an effect of the desoxycorticosterone acetate is substantiated by the fact that there was no significant retention of sodium during the growth hormone periods of the other patients. In the anabolic phase, there was a more distinct pattern of diminished urinary sodium excretion during the hormone and steroid periods and an increased excretion during the following control periods. However, there was no apparent increase in the

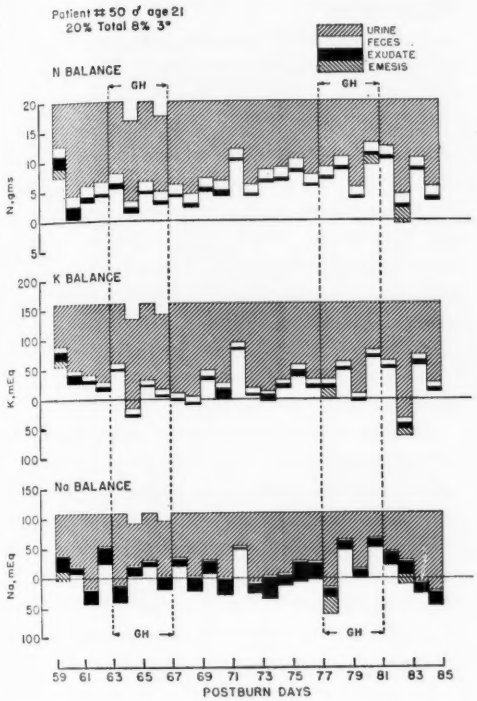


FIG. 11.

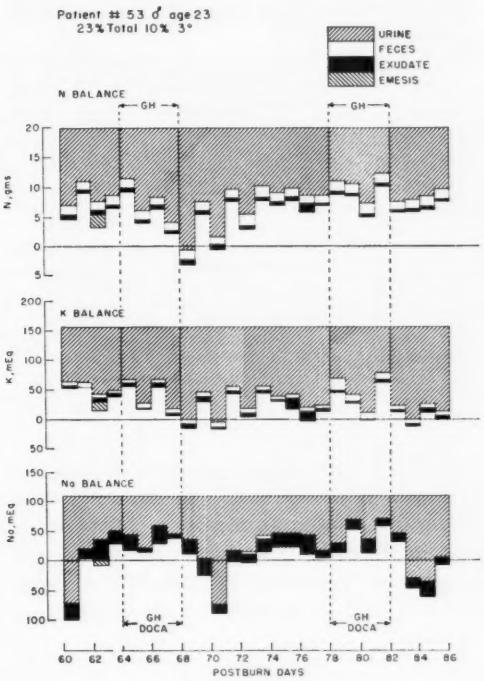


FIG. 12.

FIG. 11. Nitrogen, sodium, and potassium balances of the anabolic phase of Patient 50.
FIG. 12. Nitrogen, sodium, and potassium balances of the anabolic phase of Patient 53.

potassium output during the hormone and steroid periods of either the catabolic or anabolic phase.

Selye (16) has shown an antagonistic effect between growth hormone and cortisone upon the growth of animals and the formulation of granulation tissue. He also found that in normal and in adrenalectomized rats the administration of even small amounts of desoxycorticosterone acetate with growth hormone was associated with a greater gain in the weight of the total body, the thymus, and the spleen than when growth hormone was given alone (15). This finding suggested that there might be a synergistic effect between the two.

In patient 53, there was neither a decrease in the rate of weight loss nor an increase in the rate of weight gain during the hormone and steroid periods of the catabolic phase. However, during the anabolic phase there was a marked gain in weight during both hormone and steroid periods with an increased retention of sodium in both periods and of nitrogen in the second hormone with steroid period. It would appear that the nitrogen, potassium, and sodium balances could account for the greatest part of this weight gain.

*Potassium to nitrogen ratios.* Catabolic phase.—The cumulative balances of the control periods of the catabolic phase showed a retention of potassium and a loss of nitrogen and agreed with our earlier observations of the catabolic phase after a burn (12) (Table X). During the growth hormone periods, however, there was a cumulative negative balance of both potassium and nitrogen. The mean ratio of these losses was 3.8/1.0 and deviated from the "whole tissue" ratio of 3.0

TABLE X.—CUMULATIVE POTASSIUM AND NITROGEN BALANCES FOR CONTROL AND GROWTH HORMONE PERIODS

| *Patient No.* | *Control periods* Potassium | Nitrogen | K/N ratio | *Growth hormone periods* Potassium | Nitrogen | K/N ratio |
|---|---|---|---|---|---|---|
| | | | CATABOLIC PHASE | | | |
| 51 | +167 | − 40.6 | — | −116 | −37.0 | 3.1 |
| 52 | + 65 | − 22.3 | — | −101 | −26.5 | 3.8 |
| 54 | +110 | − 68.9 | — | −207 | −49.5 | 4.2 |
| 55 | + 90 | −109.5 | — | −330 | −96.2 | 3.4 |
| 50 | + 27 | − 31.0 | — | −145 | −38.3 | 3.8 |
| 53 | −241 | − 58.0 | 4.1 | −233 | −55.0 | 4.2 |
| | | | | | Mean | 3.8/1 |
| | | | ANABOLIC PHASE | | | |
| 51 | +293 | + 53.0 | 5.5 | +183 | +19.9 | 9.2 |
| 52 | +139 | + 38.6 | 3.6 | + 43 | +18.4 | 2.3 |
| 54 | +423 | + 58.6 | 7.2 | + 7 | +14.0 | 0.5 |
| 55 | +527 | +113.6 | 4.6 | +317 | +24.6 | 12.9 |
| 50 | +236 | + 75.9 | 3.1 | +142 | +41.5 | 3.4 |
| 53 | +302 | + 84.1 | 3.6 | +271 | +54.9 | 4.9 |
| | | Mean | 4.6/1 | | Mean | 5.5/1 |

milliequivalents of potassium to 1.0 gram of nitrogen in the direction of greater loss of potassium relative to nitrogen. This finding is often observed immediately postinjury and suggests an increased mobilization of intracellular fluid in addition to the loss of protoplasm.

Anabolic phase.—During the anabolic phase, there was a greater retention of potassium relative to nitrogen during both the control and growth hormone periods. However, since only segments of the catabolic and anabolic phases have been studied in these patients, these changes cannot be interpreted too rigorously.

The factors considered here did not create the optimum environment consistently to demonstrate an anabolic effect with bovine growth hormone in a limited number of burned patients. The intake with the highest calorie to nitrogen ratio, 6.1 grams per square meter, showed the greatest promise under the conditions of these studies, since the 9.9 grams per square meter promoted good storage with or without an anabolic agent during the anabolic phase. Limited explorations have been made to determine the effect of increasing the fat content of the diet and of administering insulin simultaneously with the growth hormone. Neither of these variables produced the desired response during the growth hormone periods.

## CONCLUSIONS

1. Significantly greater nitrogen and potassium losses were associated with the administration of growth hormone during the catabolic phase. There was a decrease in the amount of nitrogen stored on the high intake during the growth hormone periods of the anabolic phase and a variable response on the two lower levels. There were no consistent changes in the sodium and potassium balances coincident to the use of growth hormone.

2. There was a more pronounced effect upon the balances when growth hormone was given intravenously.

3. The administration of desoxycorticosterone acetate with growth hormone did not affect the nitrogen or potassium balances, but there was significantly greater sodium retention due to diminished urinary sodium excretion. In this patient, the level of 11-oxycorticoid excretion did not increase during either the anabolic or the catabolic phase.

4. There was a greater weight loss or less weight gain during the growth hormone periods except during the anabolic phase of the patient who received desoxycorticosterone acetate and growth hormone.

5. There was a rise in urinary 11-oxycorticoid excretion during most of the growth hormone periods which was most marked during the catabolic phase and was associated with greater nitrogen and potassium loss.

6. The findings during the catabolic phase confirm previous observations from this laboratory. The points of difference and their significance with regard to the anabolic phase are discussed.

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# THE EFFECT AND INTERRELATION OF TESTOSTERONE, CORTISONE, AND PROTEIN NUTRITION ON WOUND HEALING

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PROTEIN DEPLETION exerts a deleterious effect on wound healing. The factors responsible for this effect have been investigated extensively. It is not our purpose to review these studies, but certain observations are of particular interest. While impairment of tensile strength and of collagen formation have long been noted, more recent studies have demonstrated a reduction in staining reactions and in sulfation of mucopolysaccharides of the ground substance in wounds of depleted animals. Although the exact role of the mucopolysaccharides is unsettled, evidence exists that they play an essential part in collagen formation. Furthermore, diminished proliferation of fibroblasts, impaired collagen formation, and delayed gain in tensile strength have been observed in animals treated with cortisone. Here also diminution of mucopolysaccharides and defective sulfation of these complexes in the ground substance have been demonstrated. Effects of testosterone on the healing process have not been established as clearly.

This study was undertaken to determine some of the effects on wound healing of cortisone, testosterone, and both depletion and repletion of protein, alone and in combination. In addition, the anabolic action of testosterone in various states of protein nutrition, as well as the modifications of this action produced by cortisone, was evaluated in the healing wound.

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Dr. Foot is now deceased.
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## METHODS

One hundred and thirty-two young male albino rats, weighing between 200 and 300 grams, were divided into three approximately equal groups: (1) nondepleted animals maintained on a standard purina chow diet; (2) depleted animals maintained on a "protein-free" diet[1] before and after operation; and (3) depleted-repleted animals fed the protein-free diet prior to operation and the standard purina chow diet thereafter. An animal was judged to have suffered severe protein depletion when it had lost approximately 20 per cent of initial body weight—the range of 18 to 24 per cent required an average period of 20 days. Within each of the three primary groups, the animals were divided into: (a) controls, those receiving injections of normal saline (0.1 c.c.) daily postoperatively; (b) those receiving injections of 2.5 milligrams of cortisone acetate twice daily postoperatively; (c) those receiving injections of 2.0 milligrams of testosterone propionate daily, postoperatively; and (d) those receiving both cortisone and testosterone in the daily doses mentioned postoperatively. All injections were administered intraperitoneally.

[1]Corn starch 70 per cent, cellulose 15 per cent, vegetable oil 10 per cent, salt mixture 4 per cent, and cod liver oil 1 per cent with added B complex vitamins.

TABLE I.—WOUND TENSILE STRENGTH AND CHANGES IN BODY WEIGHT

| Group | 5 days after wounding: Tensile strength in grams | Weight change: *Before wounding | †After wounding | *Total | 10 days after wounding: Tensile strength in grams | Weight change: Before wounding | After wounding | Total |
|---|---|---|---|---|---|---|---|---|
| Nondepleted | | | | | | | | |
| Controls | 695 | — | + 4 | — | 1171 | — | +12 | — |
| Cortisone treated | 387 | — | −16 | — | 1002 | — | + 3 | — |
| Testosterone treated | 779 | — | +17 | — | 1071 | — | +14 | — |
| Cortisone and testosterone treated | 376 | — | + 3 | — | 1035 | — | +19 | — |
| Depleted | | | | | | | | |
| Controls | 326 | −22 | − 7 | −27 | 678 | −21 | − 9 | −31 |
| Cortisone treated | 302 | −22 | − 7 | −28 | 821 | −21 | − 6 | −27 |
| Testosterone treated | 231 | −21 | − 1 | −23 | 805 | −21 | − 6 | −27 |
| Cortisone and testosterone treated | 172 | −21 | − 2 | −23 | 756 | −20 | − 8 | −28 |
| Depleted-repleted | | | | | | | | |
| Controls | 241 | −21 | +23 | + 1 | 998 | −20 | +35 | +15 |
| Cortisone treated | 190 | −20 | +14 | − 7 | 834 | −20 | +28 | + 8 |
| Testosterone treated | 414 | −23 | +17 | − 6 | 939 | −20 | +34 | +13 |
| Cortisone and testosterone treated | 215 | −22 | +14 | − 8 | 725 | −21 | +23 | + 2 |

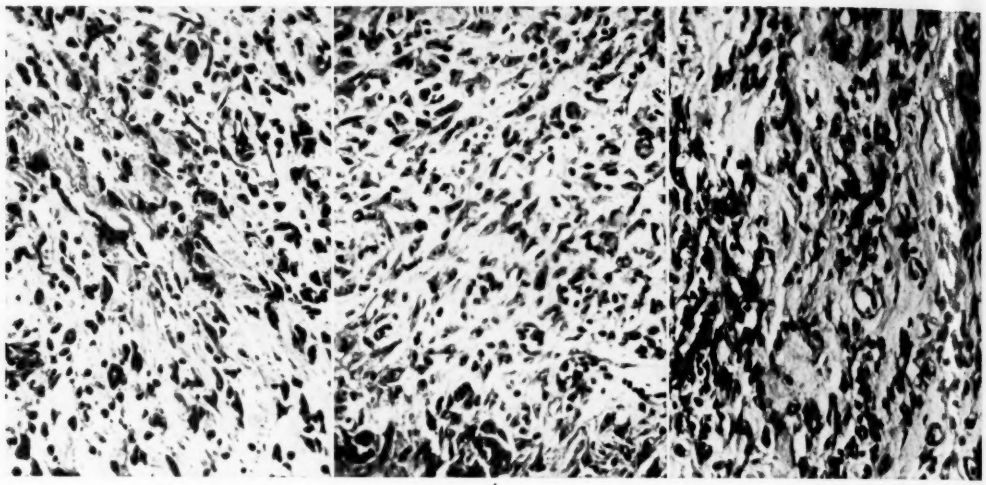
*As per cent of initial weight, averaged.
†As per cent of weight at operation, averaged.

Under light sodium pentobarbital anesthesia, a left paramedian incision 4 centimeters in length was made through all layers of the abdominal wall and was immediately closed with interrupted sutures of stainless steel wire. On the fifth postoperative day, one-half the rats in each group were sacrificed, and the remainder were sacrificed on the tenth postoperative day. Immediately after sacrifice, the abdominal wall containing the healing wound was excised and allowed to contract, and the sutures were removed. A transverse strip 1 centimeter wide was taken from the center of each wound and suspended vertically between small aluminum clamps. A beaker attached to the lower clamp was filled with water at a constant rate until the wound parted. The weight required to disrupt the wound completely was taken as a measure of its tensile strength.

The remaining portions of each wound were fixed in formalin for histologic sections. The tissues were stained with: (a) hematoxylin and eosin; (b) Masson's trichrome stain to demonstrate collagen; (c) silver impregnation of Foot and Foot to demonstrate reticulin; (d) toluidine blue to evaluate metachromasia of the ground substance which is thought to be dependent on free sulfate groups of mucopolysaccharides; and (e) Hale's colloidal iron stain, as modified by Rinehart and Abul-haj, to demonstrate mucopolysaccharides. Each of the histologic slides was evaluated by one of us (N.C.F.), and each component feature graded by plus values on a comparative basis with some necessary modifications introduced on the basis of extensive experience with these histologic techniques.

## RESULTS

*Nondepleted animals.* Among the control animals, the tensile strength of 5 day old wounds was 59 per cent of the tensile strength of 10 day old wounds (Table I). There was a slight increase over initial body weight at 5 days and a gain of 12 per cent at 10 days after operation. The younger wounds showed abundant fibroplasia and new vessel formation, and some leucocytic infiltration. There were considerable and approximately equal quantities of young collagen fibers (Fig. 1a) and reticulin (Fig. 4a). Metachromasia to toluidine blue was slight, while a moderate amount of mucopolysaccharide was revealed by the colloidal iron stain (Fig. 2a). In the older wounds there was a moderate decrease in vascularity and in the number of fibroblasts, and slightly diminished leucocytic infiltration. The compact fibers of collagen (Fig. 3a) greatly exceeded those of reticulin. While metachromasia was similar to that in the younger



a b c

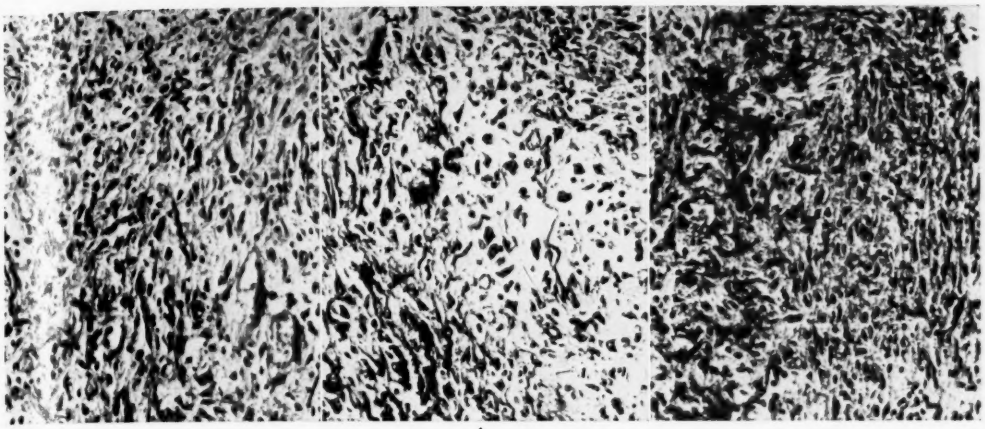
FIG. 1. Photomicrographs of 5 day old wounds of nondepleted animals. Masson's trichrome stain. ×139. a, Control. Fibroplasia and young collagen fibers are evident. b, Cortisone treated. Fibroplasia is diminished and collagen is barely evident. c, Testosterone treated. Note the abundant fibroplasia and collagen formation.

wounds, colloidal iron staining material was considerably less (Table II).

Striking changes were observed in animals receiving cortisone. At 5 days, wound tensile strength was only about half that of controls, and body weight had decreased 16 per cent. The impaired wound healing in these animals was evident histologically since fewer fibroblasts were present, reticulin and collagen formation were retarded (Fig. 1b), and smaller amounts of mucopolysaccharides were present (Fig. 2b). However, by 10 days the impairment of wound healing was much less evident, and the initial loss of body weight had been regained. Microscopically, collagen was almost equivalent to that of the controls, but impaired healing was signified by a greater proportion of reticulin.

Also striking were the effects of testosterone administration. Wound tensile strength was greater than that in control animals and body weight had increased 17 per cent 5 days postoperatively. New vessel formation, fibroplasia, and reticulin formation equalled, while the formation of collagen exceeded that of the controls (Fig. 1c). Metachromasia and colloidal iron staining also were greater than in control animals (Fig. 2c). However, by 10 days the beneficial effect on tensile strength was no longer evident and body weight was actually slightly less than at 5 days after operation. Histologically, only a greater amount of reticulin made these wounds unlike controls.

The effect of simultaneous administration of cortisone and testosterone is of particular interest because, although loss of body weight was prevented, the tensile strength of 5 day old wounds was impaired as greatly as in animals receiving cortisone alone. The adverse effect on healing was reflected in impaired collagen formation and the predominance of reticulin, although fibroplasia was plentiful. Nevertheless, metachromasia and colloidal iron staining were greater than in control animals, being comparable to that of animals treated with testosterone alone. By 10 days, the weight gain of these animals was, in fact, somewhat greater than that of controls, and the tensile strength and histologic features were comparable to those in animals treated with cortisone or testosterone alone.



a b c

FIG. 2. Photomicrographs of 5 day old wounds of nondepleted animals. Hale's colloidal iron stain. ×139. a, Control. A moderate amount of mucopolysaccharide is indicated by the dark intercellular staining. b, Cortisone treated. Minimal dark staining material is apparent. c, Testosterone treated. Note the abundant dark intercellular staining.

*Depleted animals.* Protein depletion had an extremely deleterious effect. Tensile strength of 5 day old wounds of control animals was less than half that of the nondepleted animals, and loss of body weight continued. Fibroplasia and new vessel formation were depressed, collagen was sparse and fibrillar, and the formation of reticulin was impaired (Fig. 4b). Metachromasia was slight, and small amounts of mucopolysaccharides were demonstrated by the colloidal iron stain. At 10 days the deleterious effect of protein depletion was equally evident. A further slight loss of weight had occurred. Tensile strength and collagenesis (Fig. 3b) were similar to those of 5 day old wounds of nondepleted controls. Fibroblasts were few, reticulin was prominent, and the quantity of mucopolysaccharides was minimal.

The administration of cortisone had little effect on tensile strength or body weight when compared to depleted controls 5 days after operation. By 10 days there was no further loss of body weight, and tensile strength was actually greater than in the depleted control animals.

The effect of testosterone in depleted animals was marked by prevention of further weight loss at 5 days after wounding, but there was no beneficial effect on tensile strength. At 10 days, weight loss was slightly less, while tensile strength was greater than in controls, and comparable to that of cortisone treated animals.

The depleted animals receiving both cortisone and testosterone had minimal weight loss at 5 days after operation, as did those animals receiving testosterone alone, but the impairment of tensile strength was even greater. The weight loss at 10 days after operation was similar to that of animals receiving either cortisone or testosterone, while tensile strength was slightly less than in either of these groups.

The administration of neither cortisone nor testosterone, singularly or in combination, significantly altered the microscopic features of the wounds in the depleted animals either at 5 or at 10 days, as compared to the control animals.

*Depleted animals, repleted after operation.* Protein repletion resulted in a rapid gain of body weight in all groups of animals. This was most marked in the control rats, although no beneficial effect on wound tensile strength was evident at 5 days, the actual value being less than that of depleted animals. Microscopically, fibroblasts were

TABLE II.—MICROSCOPIC FEATURES OF WOUNDS

| *Group* | *Day of sacrifice* | *Fibroblasts* | *Collagen* | *Reticulin* | *Toluidine blue metachromasia* | *Halé's colloidal iron staining* |
|---|---|---|---|---|---|---|
| Nondepleted | | | | | | |
| Controls | 5 | ++++ | ++ | ++ | + | +++ |
| | 10 | ++ | ++++ | + | ± | + |
| Cortisone treated | 5 | +++ | + | + | + | ++ |
| | 10 | ++ | ++++ | ++ | ± | + |
| Testosterone treated | 5 | ++++ | +++ | ++ | ++ | +++ |
| | 10 | ++ | ++++ | ++ | ± | + |
| Cortisone and testosterone | 5 | ++++ | + | + | ++ | +++ |
| | 10 | ++ | ++++ | ++ | ± | + |
| Depleted | | | | | | |
| Controls | 5 | ++ | + | ++ | + | + |
| | 10 | + | ++ | +++ | + | + |
| Cortisone treated | 5 | +++ | + | ++ | + | + |
| | 10 | ++ | ++ | +++ | + | + |
| Testosterone treated | 5 | +++ | + | ++ | + | + |
| | 10 | + | ++ | +++ | ++ | + |
| Cortisone and testosterone | 5 | ++ | + | ++ | + | + |
| | 10 | + | ++ | +++ | + | + |
| Depleted-repleted | | | | | | |
| Controls | 5 | ++ | + | ++ | + | ++++ |
| | 10 | ++ | ++++ | + | ± | + |
| Cortisone treated | 5 | ++ | + | ++ | + | ++ |
| | 10 | +++ | +++ | +++ | + | + |
| Testosterone treated | 5 | ++++ | ++ | +++ | + | ++++ |
| | 10 | +++ | ++++ | +++ | + | ++ |
| Cortisone and testosterone | 5 | ++ | + | ++ | ± | +++ |
| | 10 | +++ | +++ | +++ | + | ++ |

not abundant, new vessel formation was inconspicuous, and collagen formation was impaired (Fig. 5a). Whereas metachromasia was only slight, large amounts of mucopolysaccharide were demonstrated by the colloidal iron stain. However, by 10 days the beneficial effect of protein repletion on wound healing was wholly apparent in controls because tensile strength was much greater than in depleted subjects and approached 85 per cent of that of nondepleted animals. At the same time, the gain in body weight continued and resulted in a 35 per cent increase from the time of operation. Histologically, the wounds of these animals were similar in all respects to those of nondepleted controls.

In the rats receiving cortisone, weight gain was less striking. As in controls, any beneficial effect of protein repletion on wound healing was not evident at 5 days, since the tensile strength was actually less than that of depleted animals treated with cortisone. Microscopic features of these wounds (Fig. 5b) were much the same as controls except for smaller amounts of the material stained by colloidal iron. By 10 days, tensile strength was no greater than in depleted animals receiving cortisone although body weight had continued to increase rapidly. Fibroblasts were more numerous, but collagen formation was less than in repleted controls, and the proportions of collagen and reticulin were nearly equal. Mucopolysaccharides demonstrated by the colloidal iron stain were present in approximately the same small quantity as in control subjects, whereas metachromasia to toluidine blue was slightly greater.

The administration of testosterone to the repleted animals had a favorable effect, since wound tensile strength was nearly twice that of control repleted animals. The gain in body weight was somewhat less than controls at this time, but greater than that of cortisone treated animals. The proliferation of fibroblasts was marked, and reticulin and young collagen fibers were abundant in animals receiving testosterone (Fig. 5c). Toluidine blue metachromasia and colloidal iron staining were comparable to controls. Ten days postoperatively, body weight gain

a b

FIG. 3. Photomicrographs of 10 day old wounds of control animals. Masson's trichrome stain. ×210. a, Nondepleted. Dense compact fibers of collagen are evident. b, Depleted. The paucity of collagen is striking.

was approximately the same, while wound tensile strength was slightly less than that of control repleted animals. Fibroblasts were numerous and collagen formation copious in the testosterone treated animals, although a great deal of reticulin was still evident. Similarly, metachromasia was moderate, and colloidal iron staining was greater than in control repleted animals. Thus, testosterone did not increase the maturity of the wounds at 10 days as compared to the controls.

The wound tensile strength and weight gain of repleted rats treated with both cortisone and testosterone were much the same as those of animals treated with cortisone alone at 5 days after wounding. Fibroplasia and collagen formation were similar to those of cortisone treated animals, while metachromasia was less and colloidal iron staining was slightly greater. By 10 days the gain in body weight was less than that of animals receiving cortisone alone, and wound tensile strength was no greater than that of depleted animals receiving both cortisone and testosterone. Fibroplasia and the formation of collagen were similar to those of repleted animals treated with cortisone alone, while colloidal iron staining material was greater and was parallel to that of testosterone treated rats. Metachromasia to toluidine blue was slight.

## DISCUSSION

There are few previous reports on the effects of testosterone on granulation tissue formation and wound healing. In animals given testosterone systemically, Taubenhaus and Anromin noted impaired formation of granulation tissue surrounding turpentine abscesses. They postulated that this effect was due to suppression of pituitary growth hormone, since stimulation of granulation tissue production had been noted during

parenteral administration of growth hormone and was also noted about locally applied testosterone. In contrast, Loddi and Moggi reported increased tensile strength and collagen formation in wounds of experimental animals treated with testosterone systemically.

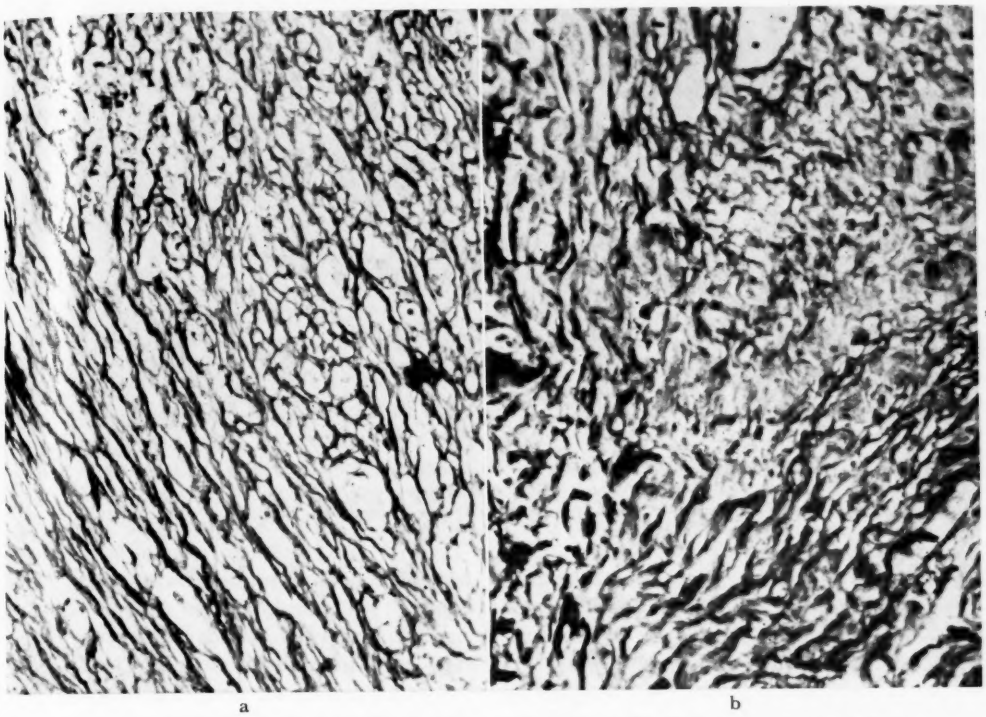
Initial acceleration of wound healing in nondepleted rats by the administration of testosterone has been demonstrated in this study. This effect is probably a result of the anabolic action of testosterone. Supporting this explanation is the gain in body weight of these animals which was greater than that of controls initially and is attributable chiefly to protein deposition. Whether suppression of pituitary growth hormone occurred in these animals and the relation of this to protein deposition and collagenesis can be determined only by further study.

Augmentation of healing was even more striking in testosterone treated animals during recovery from protein starvation as the tensile strength of these wounds was nearly twice that of controls at 5 days after wounding. In this instance, the anabolic action of testosterone is probably also responsible since an accelerated and increased protein assimilation during testosterone administration has been demonstrated in rats during recovery from fasting.

Observations on colloidal iron staining and metachromasia to toluidine blue in these wounds afford additional information on the role of testosterone. Normally the content of mucopolysaccharides in wound tissue, estimated from the intensity of colloidal iron staining, increases initially and then declines as collagen formation proceeds. Similarly, metachromatic staining to toluidine blue is normally quite evident in the earlier stages of wound healing and gradually decreases as collagen is formed. Present evidence suggests that toluidine blue metachromasia is dependent on free sulfate groups of mucopolysaccharides. In nondepleted animals treated with testosterone, colloidal iron staining material was more abundant, and metachromatic staining in 5 day old wounds was greater than in controls. Because of greater initial acceleration of healing in repleted rats, it is possible that a greater intensity in mucopolysaccharide staining reactions might also be evident in animals treated with testosterone at earlier stages of healing. Whatever the role of mucopolysaccharides in the healing of wounds, whether essential to collagen formation or important after sulfation for interfibrillary cementing of connective tissue, their importance is nevertheless indicated by the sequential changes observed in normal wounds. Initial acceleration of these changes in nondepleted animals treated with testosterone is suggested by the observations in this study and is attributable, most likely, to the anabolic action of this hormone. Whether this action is nonspecific, or involves individual effects on mucopolysaccharide synthesis and sulfation or on the formation of collagen is not known.

The beneficial effect of testosterone on wound healing is not sustained, however. The tensile strength and microscopic features of 10 day old wounds of both nondepleted and repleted rats indicated no favorable effect from the administration of testosterone when compared to controls. This is consistent with the observation of Kochakian and associates (3, 4) that increased and accelerated assimilation of protein in testosterone treated rats is of short duration, both in normal rats and in those recovering from starvation.

Certain features of impaired healing during protein deprivation are evident, although precise explanations of these phenomena are not available. Delayed formation of reticulin and collagen was evident in the wounds of these animals, and this delay was not altered by the administration of testosterone. This is not surprising, since the essential substances necessary for anabolism are undoubtedly diminished during protein starvation. Retarded synthesis or impaired accumulation of mucopolysaccharides in the ground substance may occur since a paucity of these substances as demonstrated by col-



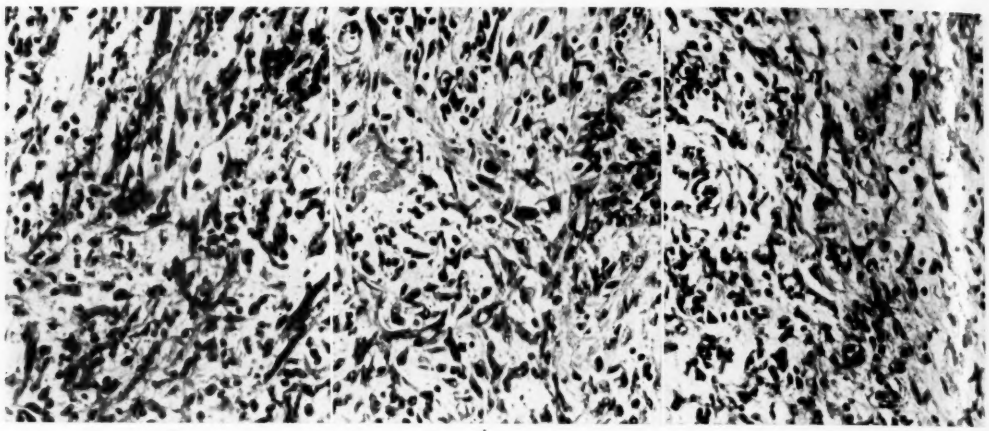
a b

FIG. 4. Photomicrographs of 5 day old wounds of control animals. Silver impregnation of Foot and Foot. ×207. a, Nondepleted. Note the abundant reticulin fibers. b, Depleted. The impairment of reticulin formation is marked.

loidal iron staining was evident at 5 days after wounding. Defective sulfation of mucopolysaccharides in protein depleted rats was suggested by Edwards and Dunphy from their observation of diminished or absent metachromatic staining and subsequent demonstration of low uptake of radioactive sulfate in the wounds of these animals. Our observations indicated no appreciable difference in metachromatic staining of wounds of depleted and nondepleted animals, although such differences may exist and be more apparent at different stages of wound healing.

A complete understanding of the action of cortisone on connective tissue formation has not been attained. However, numerous studies clearly demonstrate that cortisone has an effect on the constituents, electrostatic charge, and permeability of the ground substance. In this study the quantity of mucopolysaccharide reflected by colloidal iron staining, 5 days after wounding, was less in nondepleted or repleted animals treated with cortisone than in controls. This finding points to an adverse effect on mucopolysaccharide production or its accumulation in injured tissues. Kodicek and Loewi have reported that the sulfation of mucopolysaccharides is inhibited by cortisone, although evidence of this fact, as reflected by decreased metachromatic staining, was not obtained in the present study.

The impairment of wound healing by cortisone administration in nondepleted animals was not nearly so striking at 10 days after wounding. This fact may be attributable to a predominance of cortisone effect on the early stages of healing so that subsequent collagen formation is relatively



a b c

FIG. 5. Photomicrographs of 5 day old wounds of repleted animals. Masson's trichrome stain. ×139. a, Control. Retarded formation of fibroblasts and collagen is apparent. b, Cortisone treated. Impaired fibroplasia and collagenesis are equally evident. c, Testosterone treated. Note the abundant fibroblasts and young collagen fibers.

normal. Factors accounting for the initial loss of body weight in nondepleted rats and the return to preoperative levels by 10 days were not investigated. However, this may be a result of depletion of body protein which is gradually compensated by retention of fluid. The relation of these changes to the healing process is not clear.

It has been suggested by Findlay and Howes that the detrimental effect of cortisone on wound healing is greater in the presence of protein depletion. This theory was not borne out by our findings, since the histologic features of wounds of cortisone treated animals were similar to controls, and tensile strength was slightly greater. The explanation of this finding is not apparent but may be related in some way to adrenal atrophy which occurs during protein starvation. A similar observation was made by Pernokas, Edwards, and Dunphy who noted that cortisone, in dosages ordinarily inhibiting collagen synthesis, had no effect on the formation of collagen in adrenalectomized rats. Metabolic factors accounting for these effects have not been identified; however, several observations indicate possible explanations. In depleted states, a priority of wounds for materials essential to healing might be expected. Nonetheless, this may not be true, since the studies of Edwards and Dunphy have indicated that priority does not exist in at least one process concerned in wound healing, that of mucopolysaccharide sulfation. Then, if the effect of cortisone is greatest on rapid metabolic processes, its action might be obscured or even absent in wounds of depleted animals. Next, a growing body of evidence suggests an interrelation of protein nutrition, ascorbic acid metabolism, and adrenocortical function in wound healing. In protein depleted animals, ascorbic acid concentration of granulation tissue is low. In addition, depletion of adrenal ascorbic acid occurs, and adrenal atrophy develops. Methionine administration partially corrects these abnormalities and thus indicates that the defective repair of wounds during protein depletion may be due, in part, to impairment of synthesis of ascorbic acid and adrenocortical steroids. Thus, an alteration of the relative proportion of adrenal hormones may alter the effect of cortisone.

Two observations on the effect of simultaneous administration of testosterone to cortisone treated rats are of particular in-

terest. Although the weight loss observed at 5 days in the rats treated with cortisone alone was prevented in both nondepleted and depleted animals, no beneficial effect on wound healing was evident when compared to animals treated with cortisone alone. This finding reflects the different modes of action of the two hormones and indicates a priority or predominance of cortisone effect on the metabolic processes of healing wounds. However, it should be noted that the diminution of colloidal iron stained material in wounds of cortisone treated rats was partially offset by the simultaneous administration of testosterone.

In the tensile strength measurements recorded in Table I, no allowance was made for differences in body weight. The average initial body weight of all groups of animals was approximately the same, and analysis of the data on the basis of the ratio of tensile strength to body weight at sacrifice did not warrant any change in interpretation of results. The thickness of the abdominal wall might also be considered since tensile strength is proportional to the cross sectional area. However, as the greatest factor altering the thickness of the abdominal wall in these animals was the subcutaneous and properitoneal fat layers which contribute least to the tensile strength of the wound, calculation of tensile strength on the basis of cross sectional area did not seem justified.

In this experimental study, as in most others dealing with hormonal effects on granulation tissue formation or wound healing, the dosages of testosterone and of cortisone were higher in relation to body weight than are usually considered therapeutic in the human being. The extent to which this fact affects the results obtained can be determined only by further study.

The limited number of rats in each of the smallest groups studied does not permit an analysis of the results in terms of statistical significance; however, certain effects were sufficiently consistent and striking to suggest that they may be valid despite these limitations. Histologic and histochemical techniques, while very helpful in the study of such processes, are to some extent subjective and, of necessity, have limitations in respect to interpretation of biochemical changes. Quantitative analysis of the constituents of healing tissues would be of value in defining the effects of these hormones more precisely.

## SUMMARY

A study was made of some of the effects on wound healing of testosterone, cortisone, and both depletion and repletion of protein, alone and in combination.

In nondepleted rats acceleration of healing by the administration of testosterone was evident at 5 days after wounding. However, this effect was not sustained since collagenesis, estimated from histologic sections, and tensile strength of 10 day old wounds were slightly less in testosterone treated animals than in controls. In animals treated with cortisone, the initially marked impairment of healing was not so evident by 10 days after wounding. Simultaneous administration of cortisone and testosterone produced no beneficial effects on healing when compared to animals treated with cortisone alone.

In protein depleted animals severe impairment of wound healing was evident. Administration of either cortisone or testosterone alone did not alter this deleterious effect initially, although further impairment of wound healing was present when these hormones were used simultaneously. By 10 days, a beneficial effect on wound healing in animals receiving either testosterone, cortisone, or both, was suggested by tensile strength measurements but was not demonstrable histologically.

During recovery from protein starvation wound healing remained impaired in control animals initially, whereas tensile strength and collagenesis were strikingly increased in wounds of testosterone treated animals. Again, as in nondepleted animals, this effect of testosterone was not sustained. The impairment of wound healing in animals receiving cortisone alone or in combination

with testosterone was comparable to that in nondepleted subjects.

The evaluation of the quantity of mucopolysaccharides as demonstrated by Hale's colloidal iron stain suggests that testosterone initially may increase the formation or accumulation of these substances in wounds of nondepleted rats. Whether this represents a specific effect or is a result of the general anabolic action of testosterone has not been determined.

In the presence of protein depletion minimal amounts of mucopolysaccharides were revealed by the colloidal iron stain in 5 day old wounds. This finding was not altered by testosterone or cortisone administered singly or in combination.

In both nondepleted and repleted animals treated with cortisone, colloidal iron stained material was less in 5 day old wounds than in the control animals or in those treated with testosterone alone. However, simultaneous administration of testosterone and cortisone increased the quantity of demonstrable mucopolysaccharide although no beneficial effect on the formation of collagen or tensile strength was evident.

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# THE EFFECT OF GASTROENTEROSTOMY ON GASTRIC SECRETION

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THE EFFECT of gastroenterostomy on gastric secretion was studied years ago when it became apparent that the incidence of marginal ulcer was extremely high. Not more than 20 per cent of patients after gastroenterostomy are free of acid 6 months postoperatively, and in 60 per cent there is hyperacidity or normal acidity. In animals no stimulating effect was demonstrated, although it was noted that in some dogs marginal peptic ulcer developed, a circumstance that does not normally occur. When gastroenterostomy again became a common surgical procedure, this time in combination with vagotomy, the problem was studied again.

This procedure can best be investigated in the experimental animal by using gastric pouch secretion as an index of stimulation under varying conditions. Thus Dragstedt and his group (4) found a marked increase in Heidenhain pouch secretions in dogs if the gastroenterostomy was performed to the body of the stomach. A stoma in the region of the antrum (antiperistaltic) resulted in a slight but statistically insignificant decrease in pouch secretion. If the antrum was excised, no effect was noted with the stoma in either position, the indication being that the mechanism was antral in origin.

Harkins and associates (2) used a larger stoma (4 cm.—isoperistaltic) and obtained a significant increase in free hydrochloric acid secretion from Heidenhain pouches, irrespective of the position of the stoma. The increase was particularly pronounced when the gastroenterostomy was in the antral position.

The effect of the stomal diameter on acid secretion after gastroenterostomy in the region of the antrum was further investigated by Woodward and by Jones and their associates. A stoma 1 to 2 centimeters in diameter produced either no increase or only a slight increase in Heidenhain pouch secretion. A stoma 4 centimeters in diameter caused a marked increase in secretion. Woodward performed an antiperistaltic anastomosis, whereas that of Jones was isoperistaltic.

Thus it would appear that a small stoma does not increase secretion, probably because it does not divert a significant percentage of the gastric or duodenal contents. A larger stoma increases secretion markedly, particularly if situated in the antral region. Is it possible to avoid this stimulating effect by providing very free, almost immediate, drainage of the stomach? There is some suggestion that pyloroplasty does not increase acid secretion. We elected to fashion a very large stoma close to the pylorus and measure its influence on secretion, as compared to a stoma of similar size situated well away from the antrum. The reasons for this will be discussed later.

## METHODS

Nine healthy adult mongrel dogs were used for this experiment. A denervated Heidenhain pouch was fashioned from the fundus and body of the stomach in each animal. The diet was standard for all animals and was supplemented daily by 0.5 gram of sodium chloride. After a recovery

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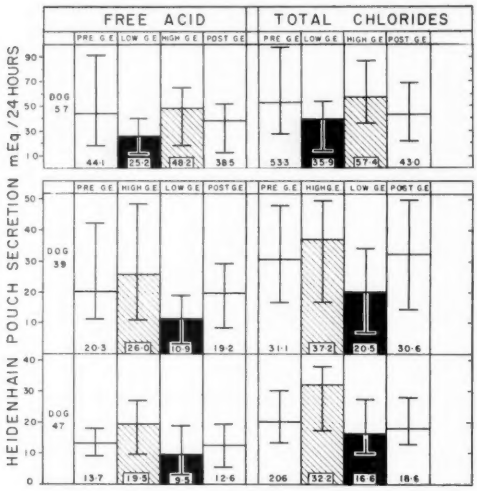


FIG. 1. Average Heidenhain pouch secretion after the procedures described, expressed as milliequivalents per 24 hours of free acid and total chlorides. The range of daily variation in secretion is also shown.

period of 30 days, continuous 24 hour secretions from the Heidenhain pouches were collected for 21 to 30 days.

In 5 dogs gastroenterostomies to the antrum were made. All anastomoses were antecolic, antiperistaltic, 10 centimeters from the ligament of Treitz, and 1 centimeter proximal to the pylorus. All stomas were 6 centimeters or over in diameter. After a 1 month postoperative recovery, daily 24 hour pouch collections were again made for 21 to 30 days.

After this collection period the anastomosis to the antrum was taken down and a new gastroenterostomy performed between jejunum and the fundus of the stomach. Again the jejunal loop was antiperistaltic and antecolic, and the stoma was 6 centimeters or more in diameter. After a 1 month recovery of the animals, pouch collections were made as before.

Two of the dogs were then subjected to a final operation in which the second anastomosis was taken down and jejunal continuity re-established. Collections of secretions from the Heidenhain pouch were again made.

In 4 dogs the initial anastomosis was to the fundus, identical to that performed as a secondary procedure in the first group. In 2 of these dogs the high position was then replaced by a low one and this was followed by its takedown.

Roentgenograms after barium ingestion were taken in 2 animals of each group. Free acid and total chlorides were collected and were calculated as milliequivalents per 24 hours.

## RESULTS

In all 9 dogs pouch secretion decreased after low antral gastroenterostomy. Secretion after high gastroenterostomy invariably exceeded that of the antral gastroenterostomy.

We believe that our results are particularly valid when the pouch secretion after both gastroenterostomy positions and subsequent takedown returns to its pregastroenterostomy level. In 3 dogs of our series this situation applied. In the remaining animals pouch secretions did not return to pregastroenterostomy levels when gastrointestinal continuity was finally re-established, or the animal succumbed before all stages of the procedure were completed. In all 3, secretion after high gastroenterostomy exceeded pregastroenterostomy levels; the results are illustrated in Figure 1. The percentage change in secretion of acid based on the pregastroenterostomy levels is shown in Figure 2.

Serial roentgenograms of animals with a low gastroenteric anastomosis demonstrated barium leaving the stomach into the distal jejunal loop before any had entered the duodenum. Most of the barium was evacuated after 20 minutes and there was no evidence of stasis in these animals. On the other hand, roentgenograms of gastroenteric anastomoses in the high positions showed rapid emptying of the proximal portion of the stomach but considerable retention of barium in the distal part after 40 and 60 minutes. A circular movement of the barium through duodenum, proximal jeju-

nal loop, antrum, and back into duodenum was suggested.

## DISCUSSION

Gastroenterostomy might be expected to stimulate gastric secretion by one or more of the following mechanisms: (1) Diversion of alkaline duodenal contents into the antral area would raise *p*H and consequently stimulate acid secretion. The influence of *p*H changes in the antral area on acid secretion has been thoroughly investigated and discussed in recent years. (2) Acid entering the duodenum normally inhibits the further production of acid, and this mechanism is interrupted by gastroenterostomy. (3) Should circus movement of food occur there would be repetitive stimulation of the antrum. (4) It is a well recognized fact that stasis of food in the antral region stimulates gastric secretion.

Gastroenterostomy might reduce gastric secretion if stasis of food in the antral region was minimized by prompt and efficient gastric drainage.

Presumably all of these factors (and probably others not yet elucidated) may modify the humoral phase of acid secretion after gastroenterostomy. Whether acid secretion is increased, decreased, or unchanged depends on the summation of these influences, and it is to be expected that the effect of gastroenterostomy on secretion will vary if stomal size and position are modified. Another possible factor which has not been studied is the question of an isoperistaltic versus an antiperistaltic anastomosis. It is unlikely that this is significant, but if it influences the factors mentioned it may well make an important difference.

Thinking in terms of antral *p*H we were surprised that a large low gastroenteric anastomosis did not stimulate, whereas the fundal anastomosis did so. The behavior of the barium, however, probably explains our results. With a low stoma the stomach emptied rapidly, whereas in the case of a high stoma there was a significant delay in emptying.

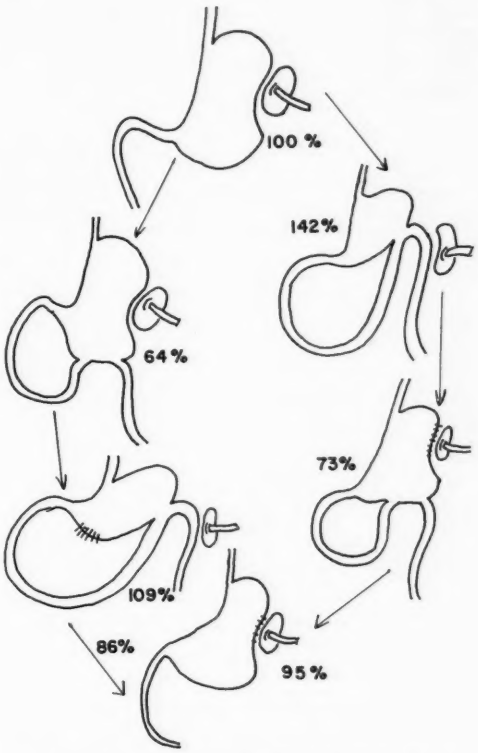


FIG. 2. The same data as in Figure 1 expressed as percentage change in pouch secretion of acid.

Thus if the stimulating effect of gastroenterostomy on gastric secretion is to be avoided stasis of gastric contents must be prevented. It is suggested that effective gastric emptying is best accomplished by a large prepyloric stoma.

## SUMMARY

1. Gastroenterostomy per se may stimulate gastric secretion and predispose to marginal ulcer.

2. At least four mechanisms influencing gastric secretion may be involved.

3. The effect of the procedure on gastric secretion is probably the summation of these mechanisms.

4. The relative influence of these mechanisms is modified by stomal size and position.

5. It is suggested that the crucial requirement is effective gastric drainage, and that this can be best accomplished by a large prepyloric anastomosis.

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# EMBOLI IN THE SURGICAL TREATMENT OF MITRAL STENOSIS

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FOLLOWING THE INTRODUCTION of mitral valvulotomy in this country by Bailey and Harken in 1947, the surgical treatment of mitral stenosis has become widely accepted. Many thousands of patients have been operated upon with results that justify a far better prognosis, both for activity and life expectancy, than when therapy was limited to medical management. Many who have reported their results have estimated that significant improvement takes place after surgical treatment in over 70 per cent of patients. The hazard of operations, as indicated by morbidity of complications and mortality rate, appears to be relatively uniform in various clinics for comparable groups of patients. The over-all mortality rate approximates 5 per cent as determined from a number of reported series.

Contributing most to postoperative complications and fatalities are arterial emboli which originate in the left atrium. Perhaps between 35 and 40 per cent of the deaths are due to these emboli. It is a logical step, therefore, to seek ways and means to reduce the incidence of emboli associated with operations upon the mitral valve. In approaching this problem, it is important to consider the role of arterial emboli in the patient who has mitral stenosis resulting from rheumatic fever and who has not had the benefit of surgical treatment. Sir William Osler in his historic text *Principles and Practice of Medicine* wrote in 1892, "It is not uncommon at the examination (at postmortem) to find white thrombi in the appendix of the left auricle. Occasionally a large part of the auricle is occupied by an antemortem thrombus. Still more rarely the remarkable ball thrombus is found, in which a globular concretion, varying in size from a walnut to a small egg, lies free in the auricle, two examples of which have come under my observation."

Recognition of thrombi within the left auricle and its appendage and their relation to emboli led to a number of studies that collectively are the basis for estimating their incidence in the natural course of mitral stenosis. Cabot, Bull, Willius, and Askey, as well as others, emphasized that emboli were a frequent cause of death in mitral stenosis, as well as being responsible for much disability. Graham and his associates, in a detailed study of 101 patients who died because of a pronounced stenosis of the mitral valve and in whom the morphologic observations were correlated with clinical findings, noted peripheral infarctions in 49. In 33 of the 49 patients, thrombi were present in the left auricle. Thirty of the 33 patients with thrombi in the auricle had been in auricular fibrillation. Of even greater significance was their conclusion that 33 patients of the 101 died as a direct result of emboli, 26 of which were cerebral.

Any patient with rheumatic heart disease is a candidate for arterial embolism. If mitral stenosis is severe enough to require surgical correction, the likelihood of emboli is much greater. In the evaluation of each individual, evidence should be sought to confirm or refute the previous occurrence of emboli. Undoubtedly, the first emboli to enter the circulation from the left atrium are often quite small, giving rise to no symp-

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toms or to those that are minimal and transitory. Unilateral pain in an extremity, sometimes regarded as muscle cramp because of short duration, episodes of faintness and unsteadiness, and back pain with hematuria, particularly in patients with auricular fibrillation, should alert one to suspect embolization. Small emboli are usually followed by larger emboli; sometimes the interval between episodes may be months. In general, the interval diminishes with time, while the size of the emboli increases. The size and the location of the emboli determine the clinical course. An embolus of small size which reaches the brain via the carotid arteries may cause great disability, or even death.

Arterial emboli occur more frequently among patients with rheumatic heart disease than in all other conditions combined. If rheumatic heart disease has involved the mitral valve sufficiently to produce stenosis which limits the patient's activity and is associated with auricular fibrillation, then, from evidence found on a general review of this subject, we believe that over 50 per cent of such patients will either sustain considerable disability or die from arterial emboli which originated within the left atrium.

The formation of a thrombus within the left atrium is believed to be related to three changes that are attributed to rheumatic heart disease: (1) the decrease in area of the mitral valve orifice which reduces the blood flow and causes stagnation of blood within the left atrium; (2) the lack of co-ordinated action of the auricle in fibrillation to propel blood from it into the left ventricle; (3) possible changes within the endocardial surface that, when present with (1) and (2), predispose to clot or thrombus formation. There are many gradations of these three conditions, usually relative to the severity and duration of the rheumatic disease and often to the age of the patient. A greatly enlarged left auricle with scarring of the endothelium in fibrillation with a very small outlet is more likely to be the site of thrombus than is the left auricle of the rheumatic heart in a young person when there is no enlargement and rhythm is regular.

The most important of these three changes is the stenosis of the valve. Its surgical correction is rendered urgent when a thrombus is present or when there has been arterial embolization. While the occurrence of embolization is an indication for valvuloplasty, it also adds to the risk of the operation. Thus, the matter of emboli in the surgical treatment of mitral stenosis is one of wide concern as emphasized by Ellis and Harken. In recent years we have repeatedly reviewed the reported experience of others and carefully analyzed our own. The object of this endeavor has been to provide optimum protection against the hazards associated with thrombus formation in patients who are to be treated surgically for valvular disease apparently occurring in the wake of rheumatic fever. Our present over-all policy for the management of patients who had had previous emboli, or who we strongly suspect might have emboli after operation, is discussed together with the reasoning upon which it is based. A brief summary of our observations among 400 consecutive patients is presented.

For those patients whose embolic episode occurred more than 6 weeks previously, operation is embarked upon after the usual evaluation and preparation. If the time is less than 6 weeks, anticoagulant therapy is started and maintained until at least 6 weeks have elapsed. Just prior to operation, this therapy is discontinued and the prothrombin time allowed to return to normal for 24 hours or longer.

All patients with a history of previous emboli are approached as if they had thrombi within the left auricle. When the auricular appendage is exposed, care is exercised not to place a clamp across it or to dislodge any thrombic material within its lumen. Occluding purse-string sutures are carefully placed, and the tip of the auricular appendage is incised. If there is free bleeding and clots are not present, then an occluding clamp may be placed proximally and the

opening further enlarged. When thrombus material is present in the auricular appendage, it is completely evacuated. If the thrombus material is well organized and attached to the wall of the auricle so that the stenosed valve can be opened satisfactorily without disturbing the thrombus, then no attempt should be made to remove it. If the thrombus is fragmented or if it is loosely attached so that it may liberate an embolus during or after valvulotomy, then the thrombus is broken up and washed out through the auricular appendage. During these manipulations, intermittent pressure is applied to both common carotid arteries by the anesthesiologist in order that a clot or fragment of a clot, if it were dislodged and carried out into the systemic circulation, would be less apt to lodge in the brain where it would cause serious difficulty and could not be removed. With careful maneuvering, a pedunculated thrombus may be evacuated intact. It is always highly desirable to leave behind as little roughened surface as possible where a thrombus has been attached because this is a fertile field for additional thrombus formation. An evaluation of the stenosed valve is to be made before disturbing the thrombus. However, the thrombus should be removed before attacking the valve. A stenosed valve which can be opened to an area that is comparable to the normal of 4 to 6 square centimeters without sustaining regurgitation is the ideal in establishing conditions that are most likely not to be followed by further thrombus formation. It is emphasized that a stenosed valve not well opened and a surface area of fragmented thrombus or of the auricular wall to which a thrombus has been attached provides an ideal situation for new thrombus formation. If, at the same time, the blood pressure is maintained at a level lower than that which has been normal for the patient, thrombus formation may occur rather rapidly. Death has been observed to result from thrombus formation that propagated directly from a fragmented thrombus of the auricular wall through the mitral valve into the left ventricle and then into the aorta to occlude it.

Those patients with previous arterial emboli who at operation have no evidence of thrombi in the left auricle are rarely given anticoagulants after operation. There are a few situations, however, in which such therapy is recommended: The first is the association of a large left auricle in auricular fibrillation and a valve that has not been greatly increased in area or is partially incompetent, in other words, an enlarged, fibrillating auricle through which the blood does not flow readily. Second is calcification within the valve associated with calcium deposits on the valve surface. Such findings in our experience are encountered more frequently in men who have done considerable heavy physical work for a period of years in spite of a mitral stenosis. When the commissures are separated, the valve surface may be markedly roughened because of calcium deposition and scar formation. At the extremities of the newly separated commissures of the diseased and distorted valves, thrombus formation may take place. Then, third, is disease which has been diffuse and of long standing and in which there is multivalve involvement and the heart has become greatly enlarged in all chambers. The blood flow through such a heart may be little improved even when the stenosed mitral valve has been adequately and satisfactorily opened and other valves properly dealt with. The burden of the operation may further diminish the heart's efficiency so that the blood flow through it becomes markedly reduced in the immediate postoperative period. The small rough surface at the site of the commissurotomy may, under these circumstances, be a nidus for thrombus formation. For these three situations, anticoagulant therapy should be instituted as soon as the operation is completed and should be continued for at least 2 weeks and, in many instances, for 4 to 6 weeks. In the first situation, anticoagulants should be continued indefinitely.

All patients with thrombi in the left auricle or appendage should be given anticoagulant

drugs during or at the completion of the operation. If the thrombus has been small and has been completely removed, the administration of anticoagulants may be discontinued at 2 weeks. If the thrombus seemed to have been of long standing with a smooth surface and the valve has been well opened, 2 to 4 weeks of anticoagulants should be sufficient. If, however, a thrombus has been partially removed, leaving a considerable amount of roughened surface, and the stenosis has not been well corrected or insufficiency is present, then prolonged anticoagulant therapy is indicated for several weeks or months, and sometimes even indefinitely. When new embolic phenomena occur after operation regardless of whether or not there have been previous emboli or thrombi found at operation, anticoagulant therapy should be instituted and maintained for 2 months or more.

In the consideration of how thrombi form in the left auricle and its appendage, it should be stressed that several factors may play a role in this phenomenon and that these also may determine when all or part of the thrombus is liberated into the arterial circulation as an embolus. The decreased flow of blood through the stenosed valve is accompanied by currents and eddies which are produced as it courses against the closed portion of the valve. As pressure is increased, particularly during periods of exercise when the demand for increased blood flow quickly rises, the left auricle becomes distended. If the distention is marked and sustained, dilatation may result. Such an enlarged auricle is quite likely to fibrillate. When fibrillation occurs, the auricle loses its ability to empty itself efficiently. This, in turn, leads to an almost constant increased intra-auricular pressure which becomes the important force in propelling the blood flow through the stenosed mitral valve. It is a vicious cycle of events, and the result is an ever increasing pressure which is required to force the blood into the left ventricle where it can be propelled into the aorta to meet the body's demands. Of course, the increased pressure in the left auricle causes an elevation of the pressure within the pulmonary circulation. The vascular path here becomes scarred and thickened, and resistance to blood flow is increased. The burden of overcoming this is increased, and the right ventricle undergoes hypertrophy in response. If it in part fails, then the right auricle becomes enlarged and the tricuspid valve incompetent. These possibilities are mentioned here because when the mitral valve has been diseased and stenotic for a long time, the conditions favorable for thrombus formation are present. At the same time, the heart as a whole is less able to tolerate what may be imposed upon it by the liberation of an embolus into the pulmonary or systemic circulation.

Furthermore, it is suggested that mitral stenosis of any clinically significant degree which has been present for very long provides the conditions known to be favorable for thrombus formation. This fact is emphasized because it is believed that thrombus formation within the left auricle is to be anticipated in all patients with mitral stenosis. If the patient is young, the heart not enlarged, and the rate regular, thrombus formation is less likely to occur than if the patient is 20 years older and the heart is enlarged and in auricular fibrillation. Thrombus formation in the auricle precedes arterial embolization. Thrombi may exist and no emboli result. But, again, this circumstance is dependent upon several factors, any one of which may result in a thrombus being fragmented and embolization taking place. However, of these, time and severity of the disease seem most important. That patients who had frequently experienced arterial embolization and who at operation have no thrombi within the auricle are not rare is evidence that thrombi can form and be passed on into the circulation, and no further thrombus formation takes place at least for variable and often prolonged periods of time. Both thrombi without embolization and embolization without evident thrombi being encountered at operation indicate the unpredictability of

TABLE I.—DEATHS FOLLOWING OPERATIONS UPON THE MITRAL VALVE ASSOCIATED WITH SYSTEMIC EMBOLI OR THROMBI IN THE LEFT ATRIUM

| No. | Age | Sex | Rhythm | Pre. emboli | Thrombi at op. | Autopsy | Cause of death |
|---|---|---|---|---|---|---|---|
| 1 | 39 | F | A.F. | + | + | + | Cardiac arrest after removal of thrombi |
| 2 | 39 | F | A.F. | + | 0 | + | Cerebral embolus |
| 3 | 43 | F | N.S.R. | 0 | + | 0 | Multiple emboli |
| 4 | 49 | F | A.F. | 0 | + | + | Multiple emboli; hemorrhage |
| 5 | 45 | M | N.S.R. | + | + | + | Ball-valve thrombus; emboli, spleen, and kidneys |
| 6 | 42 | F | A.F. | 0 | + | + | Cerebral embolus |
| 7 | 47 | F | A.F. | 0 | + | 0 | Cardiac arrest after removal of thrombus |
| 8 | 52 | F | A.F. | 0 | + | + | Multiple emboli; G.I. hemorrhage |
| 9 | 55 | F | A.F. | 0 | 0 | + | Emboli—mesenteric |
| 10 | 42 | F | A.F. | 0 | + | 0 | Multiple emboli—renal and mesenteric |

what may occur when thrombi form within the auricle.

The incidence of arterial embolization in the natural history of mitral stenosis is looked upon as being high and very prominent as an immediate complication and cause of death. Thrombi that occlude the blood flow through the auricle and the formation of a ball-valve thrombus are relatively infrequent.

## CLINICAL MATERIAL

For a period of 7 years and 8 months, from March 1951 to November 1958, 400 patients were selected for the surgical correction of mitral stenosis. A review of this experience reveals that 123 patients (30.8 per cent) had had either arterial emboli before, during, or after operation or thrombi which were demonstrated within the left auricle or its appendage at operation. Twenty three of these patients had a normal sinus rhythm and the remaining 100 had auricular fibrillation. Twenty-two deaths, a mortality rate of 5.5 per cent, occurred in this consecutive series, either during operation or in the immediate postoperative period before discharge from the hospital. An analysis of the deaths, including careful correlation between clinical course, operative findings, and postmortem examination (68 per cent) when done, strongly indicated that arterial emboli were directly responsible for fatalities in 8 and indirectly in 2 (Table I). Thus, almost half of the deaths, 45.4 per cent, were associated with arterial emboli. In addition, among those in the remaining 101 patients who had emboli prior to operation, there was considerable disability ranging from transient, minimal sensory disturbance to irreversible hemiplegia. Because almost 1 in 3 patients selected for the surgical correction of mitral stenosis may be expected to have some complication associated with emboli, ways and means to prevent and manage these situations have become of special interest to those involved in this endeavor.

The heart in normal sinus rhythm is less frequently the site of thrombus formation than that with auricular fibrillation. At the time the operation was begun, 175 patients were in normal sinus rhythm and 225 were in auricular fibrillation. Of the former only 23 had experienced emboli or thrombi, while of the latter 100 had emboli at some time or other, or thrombi at the time of operation.

*Emboli before operation.* In the evaluation of patients being considered for operation, a history of previous emboli is of significance. Generally they are an indication for operation and are evidence that the heart has undergone definite changes commonly associated with advanced rheumatic heart disease. Of 400 patients, 82 (20.5 per cent) had evidence of a previous embolic phenomenon. There were 28 patients who had had more than one episode. Of the 82 patients, 65 (79.1 per cent) were in auricular fibrillation at the time of operation. Twenty patients in this group of 82 had thrombi at operation, an incidence of 24.4 per cent. It was the surgeon's belief that in 10 of these the removal of the thrombus was complete, and in the remaining 10 it was left unmolested or only a small portion was evacu-

TABLE II.—ANTICOAGULATION IN THE PREOPERATIVE PERIOD

| | *At any time* | *Less than 3 weeks* | *For at least 3 weeks* | | *For 6 weeks or more* | |
|---|---|---|---|---|---|---|
| | | | *Clots at op.* | | *Clots at op.* | |
| 1st 100 | 4 | 1 | 3 | 1 | 1 | 1 |
| 2nd 100 | 8 | 3 | 5 | 1 | 4 | 1 |
| 3rd 100 | 14 | 1 | 13 | 2 | 10 | 1 |
| 4th 100 | 20 | 1 | 19 | 2 | 10 | 0 |
| Total | 46 | 6 | 40 | 6 (15%) | 25 | 3 (12%) |

ated. There were 3 deaths in the group of 20, a mortality rate of 15 per cent.

*Thrombi within the left atrium or its appendage at the time of operation.* Of the 400 patients, 51 (12.8 per cent) had thrombi or clots within the left atrium or its appendage at operation. Thirty-one (7.7 per cent) of the 51 patients had no previous history of emboli. Forty-nine (12.3 per cent), or all but 2, were in auricular fibrillation. Of the 2 patients in normal sinus rhythm who had clots in the left atrium, 1 patient had a history of previous embolization and the other had no indication of previous emboli. The incidence of clots in the left atrium or its appendage among the 225 patients with auricular fibrillation was 21.8 per cent as compared to 1.1 per cent for those in normal sinus rhythm. A patient with auricular fibrillation is much more likely to have clots within the left atrium or appendage than one in normal sinus rhythm, even if there is no history of previous emboli. When present, they contribute to an increased mortality rate. There were 8 deaths in the 51 patients, a mortality rate of 15.7 per cent. These 8 represent 80 per cent of the deaths due directly or indirectly to emboli.

*Emboli during the immediate postoperative period.* Emboli occurred during the immediate postoperative period and before discharge from the hospital in 12 patients (3 per cent). These emboli were believed to be due to thrombus formation within the left auricle. In 4 additional patients the emboli were believed to be due to fragmented calcium liberated at the time of operation. Of the 12 patients believed to have intra-auricular thrombi, 2 were in normal sinus rhythm and 10 were in auricular fibrillation at the beginning of the operation. Seven of these patients died because of emboli in this postoperative period (Cases 2, 3, 4, 6, 7, 8, and 9—Table I). None of those with emboli considered to be calcific fragments died, and in most cases the disability was minimal.

ANTICOAGULANTS

In the 123 patients who had systemic emboli or had thrombi at operation, 73 (59.3 per cent) were given anticoagulants at one time or another during the course of the disease. Anticoagulants were used 3 times as frequently in the fourth 100 patients as in the first 100 patients.

Preoperatively, 46 patients received anticoagulants for a variable length of time (Table II). In 40 patients who had received anticoagulants for at least 3 weeks immediately prior to operation, clots were found at operation in 6 cases, an incidence of 15 per cent. In 25 of these 40 patients, anticoagulants had been given for a longer period of time prior to operation. In the group in which treatment was a minimum of 6 weeks, clots were found in 3 patients, or 12 per cent. This figure is almost identical with that for the incidence of clots in the entire series of 400, 12.8 per cent, but is approximately half that for the incidence of clots in those cases in which emboli occurred preoperatively, 24.4 per cent. This fact is significant when one considers that in almost every instance the anticoagulants were given preoperatively because of systemic emboli. In 33 patients who had emboli prior to operation but were not treated with anticoagulants, 11 (33.3 per cent) were found to have clots at operation. Thus, when systemic emboli have occurred prior to operation, a course of anticoagulation therapy for at least 3 weeks immediately prior to operation appears significantly to reduce the incidence of clot formation in the atrium at operation.

Postoperatively, anticoagulants were used in a total of 52 patients. In 24 cases this was a continuation of preoperative anticoagulant therapy. In another 15 patients treatment was begun for the first time because

of the finding of clots at operation. Systemic emboli in the postoperative period was the reason for starting treatment in 13 patients. Anticoagulants were given 5 patients postoperatively because of pulmonary emboli.

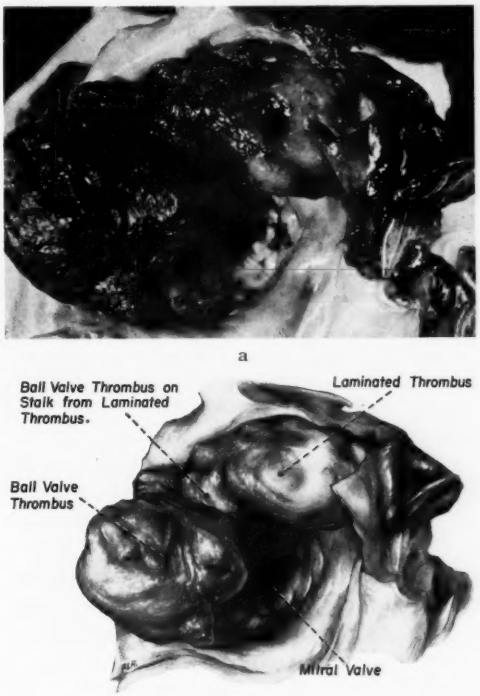
CASE REPORTS

A 45 year old male was known to have had mitral stenosis for several years. There had been increased dyspnea on exertion and occasional hemoptysis during the preceding year. There was no frank history of embolic phenomena, although the patient had suffered temporary partial loss of the visual field of the left eye 2 months prior to operation. At operation, a thrombus was found in the auricular appendage. Separate and distinct from it was another thrombus on the wall of the left auricle, extending from just above the mitral valve toward the pulmonary vein. The thrombus within the auricular appendage was removed, but the one in the auricle was not disturbed. The mitral valve was markedly calcified with great thickening and shortening of the posterior leaflet. The valve area was estimated at 1 square centimeter. This orifice was enlarged to an estimated 2.5 to 3.0 square centimeters. Because of the thrombus anticoagulant therapy was started the day after operation. The postoperative course was quite satisfactory until the third postoperative day when the patient died suddenly.

Postmortem examination revealed thromboembolism. There was a mural thrombosis of the left atrium with "ball-valve" effect (Fig. 1). A large laminated thrombus, approximately 5.0 centimeters in diameter, filled the atrial appendage and adjoining atrium. Attached to this by a slender stalk was another ball-shaped, recent thrombus approximately 5.0 centimeters in diameter which was partially wedged between the separated leaflets of the mitral valve. Microscopically, the thrombus exhibited various gradations of organization. The new thrombus was composed of blood, hyaline, and amorphous material.

There were old and recent infarcts of the kidney with wide-based cortical scars and recent wedge-shaped hemorrhagic areas of necrosis in the cortex. Microscopically, areas of old fibrous scarring and necrosis and hemorrhage suggesting infarction were present. There was a splenic infarct. At the upper pole of the spleen there was a large irregular area which was darkly hemorrhagic and of firm consistency. Histologically, this area was hemorrhagic, and the normal architecture of the tissue dense. In addition, there was chronic cholecystitis and cholelithiasis. In the right supraclavicular fossa there was scarring from a resection for carcinoma of the right salivary gland 9 years prior to death, but no evidence of tumor.

When a thrombus is present in the left auricle at the time of operation, anticoagulant therapy should be instituted immediately. Heparin, 1.0 milligram per kilogram, is used to initiate an increased bleeding time that can later be maintained on dicumarol.




a

b

FIG. 1. a, Photograph of ball valve thrombus that caused sudden death by obstructing the mitral valve on the third postoperative day. b, Artist's sketch of "a."

A 56 year old female, mother of 1 child, was known to have had mitral stenosis for 32 years and required digitalis from time to time for a period of 20 years. Six years prior to hospital admission she had an embolus to the right arm, from which she made a complete recovery. Eight months prior to admission there was an episode suggesting an embolus to the left leg, from which the patient made a satisfactory recovery. Three months prior to admission the patient had an embolus to the right femoral artery, for which an embolectomy was done and a well organized clot of cylindrical shape measuring 2 centimeters in length and 7 millimeters in diameter was removed.

When the patient was admitted to the hospital for correction of the mitral stenosis, recovery from the embolectomy was complete. The heart was markedly enlarged and its configuration typical of mitral steno-

sis. There was auricular fibrillation. At operation there was no evidence of thrombi within the auricular appendage or the left auricle. A markedly stenosed valve with an aperture of about 1.0 square centimeter without regurgitation was found. The valve leaflets were separated to provide a valve area of an estimated 3.5 square centimeters. Immediately after operation anticoagulant therapy was started and maintained for several weeks.

During the 20 months after operation, the patient's activity was gradually increased until she was able to indulge in ordinary activity to a greater extent than at any time in the past 12 years. Although she is in auricular fibrillation, there has been no evidence of any additional emboli.

Complications from anticoagulant therapy occurred in 17 cases (13.8 per cent). Of these, 10 (8.1 per cent) were considered minor and consisted of hematuria, minor vaginal bleeding, and bleeding from the gums. Major complications occurred in 6 cases, 4.8 per cent, and consisted of more severe bleeding from the operative wound and from the gastrointestinal tract as well as retinal and cerebral hemorrhage. In 3 cases, the complications were so severe that the anticoagulants were permanently discontinued. In 1 case, death on the second postoperative day was directly the result of hemorrhage occurring from the use of heparin (Table I, Case 4).

SUMMARY

In a modest experience with 123 patients who have had systemic emboli or who have had thrombi demonstrated at operation, anticoagulants have been employed in 73. Although in the early period of this endeavor the criteria for using this adjunct therapy in the surgical management of mitral stenosis were rather rigid and restrictive, it has more recently been employed routinely when certain indications were present.

It is used preoperatively when: (1) there are physical findings of previous emboli; (2) there is a history of previous embolization; (3) thrombi within the heart are suspected—on a basis of history, physical findings, or angiocardiography.

It is used postoperatively when: (1) it has been employed preoperatively; (2) thrombi are demonstrated at operation; (3) the operative procedure has exposed a rough surface, such as may result from dividing a thickened, calcium-containing valve commissure, and the heart is much enlarged and other valves are involved.

Anticoagulant therapy is accomplished as follows: (1) Preoperatively—by the administration of warfarin sodium (coumadin sodium) for 3 to 6 weeks in patients with a history of emboli; daily dose (5 to 10 milligrams postoperatively) regulated to maintain prothrombin time 2 to 2.5 times normal. The drug is discontinued 24 to 48 hours before operation and vitamin K is not given. (2) Postoperatively—by the administration of warfarin sodium (coumadin sodium) 0.6 milligram per kilogram of body weight intravenously in the recovery room and daily maintenance dose as for preoperatively. Heparin, 75 milligrams intravenously at operation and 75 milligrams every 4 to 6 hours, clotting time not to exceed 3 times normal before each injection.

We believe that anticoagulants used under these conditions will materially reduce the mortality and crippling complications from systemic emboli associated with operation for mitral stenosis.

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# SOME OBSERVATIONS CONCERNING THE PULMONIC VASA VASORUM

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THE ARTERIAL VASA VASORUM of the pulmonary vessels have been described by Miller, Verloop, von Hayek, and others as branches of the bronchial arteries. Since the bronchial arteries arise from the thoracic aorta or one of its main thoracic subdivisions, as shown by Cauldwell and associates, those branches of the bronchial arteries forming the vasa vasorum convey systemic blood rich in oxygen to the walls of the pulmonary artery and veins. The nourishment of these vessels should be related to the thickness of their walls and to the oxygen content of the blood flowing through them. It seems likely, therefore, that there would be a difference in the pattern and distribution of the vasa to these two types of pulmonic vessels, for structurally the pulmonary artery is unlike a typical systemic artery as the composition of its walls is between a systemic artery and a systemic vein and as it carries blood with low oxygen content. The pulmonary veins on the other hand have relatively thin walls and convey blood with a high oxygen content.

No specific studies have been made of: (1) the embryologic origin of the human pulmonic vasa vasorum; (2) the depth of penetration of the vasa into the walls of the pulmonic vessels; (3) the role of the vasa in organization of pulmonic thrombi or in hypertrophy of the tunica media of the pulmonary artery; and (4) the structure and distribution of the venous vasa vasorum to the walls of the pulmonary vessels and the sites at which drainage of the venous vasa occurs.

In order to enhance knowledge concerning these aspects of the pulmonic vasa vasorum, the following studies were made.

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## MATERIAL AND METHODS

To trace the development of the pulmonic vasa vasorum, serial sections of 8 human embryos, 10 to 58 millimeters in crown-rump length, were studied. The vascular system in some of these embryos was partially injected with India ink by way of the umbilical vessels.

The anatomy of the pulmonic vasa of the adult was obtained from dissections of, and microscopic sections from, the lungs of 20 male or female cadavers, ranging in age from 29 to 83 years. Parts of these dissected lungs containing the pulmonic vessels were also cleared in glycerin to facilitate study of the vasa. In 6 normal lungs obtained from autopsy, the bronchial arteries were injected—2 with liquid latex, according to the technique of Tobin, and 4 with India ink. After fixation and hardening in 10 per cent formalin, the injected lungs were also dissected, some of the pulmonic vessels were cleared in glycerin, and histologic sections were made from other areas of them.

In 25 cases of pulmonary thrombosis, microscopic sections were also studied for the source of the vessels which had grown into organizing thrombi. In addition, slides from 25 other cases without pulmonic disease and 25 cases of hypertrophy of the layers in the wall of the pulmonary artery were also studied to determine the normal and altered course and distribution of the pulmonic vasa. All of the microscopic sections were from tissues fixed in 10 per cent formalin or in Zenker's acetic, cut in paraffin at 7 or 10 microns, and stained with hematoxylin and eosin.

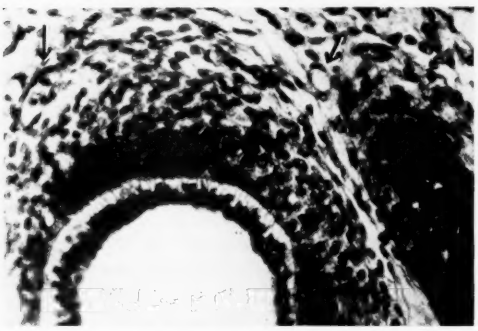

FIG. 1. Section through a bronchial wall and pulmonary artery from a human fetus of 20 millimeter crown-rump length. The pulmonary but not the bronchial artery is filled with India ink. Note branches of the bronchial artery (indicated by arrows) to the wall of the bronchus and as the vasa vasorum in the adventitia of the pulmonary artery. ×267.

OBSERVATIONS

*Embryology.* In the younger embryos, 10, 16.5, and 17 millimeters in crown-rump length, it was not possible to determine accurately whether the capillary-like vessels, which surrounded branches of the pulmonary artery, and the associated bronchi were derived mainly from branches of the pulmonary artery or bronchial artery. However, in the older embryos, 20, 26, 47, 56, and 58 millimeters in crown-rump length, branches from the bronchial artery could be traced easily to the walls of the pulmonary artery (Fig. 1) and vein, and the main source of the arterial vasa from the bronchial artery could thus be established. There were smaller arterial vasa also derived from secondary branches of the pulmonary artery.

*Adult specimens.* The pulmonic vasa vasorum in many of the lungs from the cadavers[1] were filled with clotted blood, and their course and distribution could be followed readily. By this method of study, it was apparent that the vasa were more numerous on the walls of the pulmonary artery than on pulmonary veins of comparable size (Fig. 2). At and near the hilus of the lung, the pulmonary artery was well supplied with vasa vasorum; as the artery extended into the bronchopulmonary segments, there were fewer vasa on the arteries, and that part of the pulmonary artery adjacent to an accompanying bronchus had a greater number of vasa on it than that part of the artery away from the bronchus (Fig. 3). Studies of cleared tissues also indicated that the vasa in the connective tissue around the pulmonary arteries and veins are in several strata (Figs. 4 and 5). The vasa could be traced distally along the walls of the pulmonary vessels down to those which had external diameters of 1 millimeter (Fig. 6). Microscopically, the vasa were also found to extend to the walls of some of the pulmonary arterioles and venules.

The human pulmonic arterial vasa are accompanied by parallel venous vasa. This finding is in agreement with the studies of Lowenberg and Shumacker on the vasa of the internal carotid artery, jugular vein, and aorta of dogs, and those of Short on the human femoral vein. The arterial vasa in the present studies were observed to be larger than the accompanying venous vasa (Figs. 4 and 5). This finding may have been due to the distention of the arterial vasa by the injection media, or by forcing of blood from the bronchial or pulmonary artery into the vasa by the embalming solution.

The arterial vasa were usually in the form of long tapering vessels with side branches (Fig. 6), but additional small channels from the bronchial artery on the wall of the bronchus also joined the vasa on the artery (Fig. 3). The venous vasa formed arcs or loops, and they were more irregular in their course than the arterial vasa The venous vasa on the arterial wall emptied into the bronchial veins on the accompanying bronchus, whereas the venous vasa of the pulmonary vein drained directly into that vein.

Verloop and Marchand and his associates stated that the pulmonic vasa do not empty into the lumen of the pulmonary

[1]The embalming solution was injected into the right femoral artery under 5 pounds of air pressure. This solution apparently forced part of the fluid components of the blood into the vasa where it clotted.

FIG. 2.

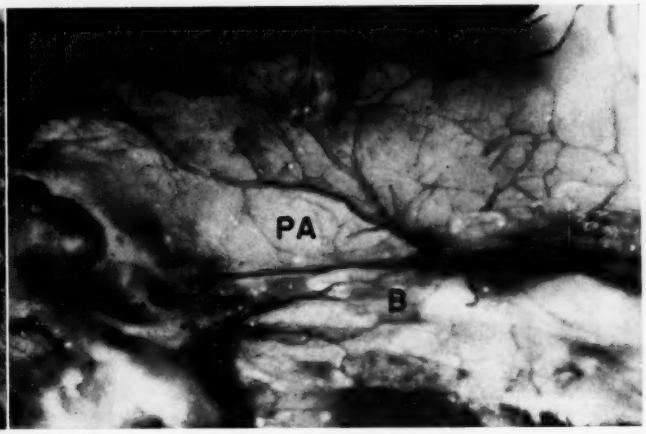


FIG. 3.

FIG. 2. Dissection of an embalmed lung from a 78 year old male who died of coronary thrombosis. Note the more numerous vasa vasorum on the walls of the pulmonary artery (*PA*) as compared with those on the branches of the pulmonary veins (*PV*). ×⅔.

FIG. 3. Part of a bronchus (*B*) and its accompanying pulmonary artery (*PA*) cleared in glycerin (from the specimen shown in Fig. 2), illustrating the larger numerous vasa vasorum on that part of the pulmonary artery adjacent to the bronchus. ×4.4.

artery, and in the present studies no branches from the injected vasa were observed to pass completely through the walls of normal pulmonary arteries or veins. However, after the injection of India ink into the bronchial artery, some of the ink was present in the lumen of the pulmonary artery which demonstrated that there are anastomoses between the bronchial arteries and the pulmonary artery in some part of their course. Ink was also found in the lumen of the pulmonary vein. If the ink had traversed the pulmonary artery and the pulmonary capillaries to get into the pulmonary vein, some of the capillaries around the alveoli should have contained the ink. Since none was found in the sections of these capillaries, the venous vasa must have conveyed the ink into the pulmonary vein. This finding is in keeping with the fact that the venous vasa are comparable to other branches of the bronchial veins which also empty into the pulmonary veins within the lungs.

As in other parts of the body, the blood vessels usually accompany nerves in neurovascular bundles. Both in dissections of the gross specimens and in sections from the pulmonary vessels, the pulmonic vasa were found to accompany branches of the nerves to the pulmonic vessels and bronchi.

The systemic vasa vasorum are usually described as only penetrating into the outer one-half of the diameter of the arterial wall. However, Benjamin, Bartenbach, and Zeit have shown that the vasa vasorum may penetrate into the media of the aorta. That the pulmonic vasa also penetrate into the middle of the tunica media was observed in sections from the pulmonary artery (Fig. 7). In addition, there may be extensions of the endothelial lining of the pulmonary artery peripherally between cells of the tunica intima into the tunica media (Figs. 8 and 9). The question then remains as to what supplies the muscle and elastic tissue in the inner layers of the tunica media, and whether these channels are continuous normally or only under certain pathologic conditions.

The vasa may traverse the entire thickness of the wall of the pulmonary artery, as demonstrated in those cases of organized pulmonary thrombosis in which branches

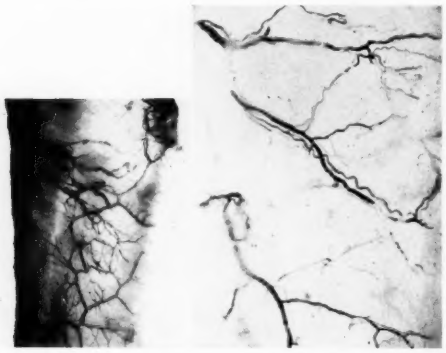

FIG. 4.



FIG. 5.

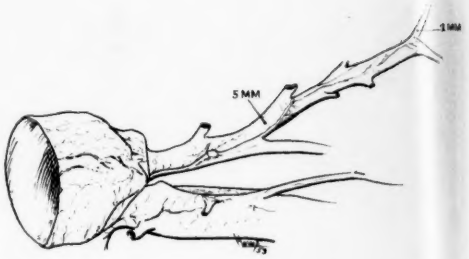


FIG. 6.

FIG. 4. Part of a pulmonary artery cleared in glycerin. The arterial vasa vasorum were injected with India ink by way of the bronchial artery. Note the branches of the arterial vasa vasorum accompanied by two smaller parallel venous vasa and the various depths of these branches in the adventitia. Specimen from an 11 year old male who died in an epileptic seizure. ×2.2.

FIG. 5. Part of a pulmonary artery, cleared in glycerin, after injection of the vasa vasorum with India ink. Microscopic sections made from this specimen showed that the arterial and venous vasa vasorum were in varying depths of the adventitia of this vessel. Artery obtained from the same specimen as shown in Figure 4. ×3.8.

FIG. 6. Drawing of part of a pulmonary artery in which the arterial vasa vasorum were injected with India ink. Note the long tapering branches of the arterial vasa. At certain points on the arterial wall additional vasa from the bronchial artery on the accompanying bronchus were added to the arterial wall. The diameters of the bronchial branches, at various levels, are indicated.

of vessels may be followed either as capillaries or as arterioles and venules from the vasa vasorum through the wall of the pulmonary artery into the thrombus (Figs. 10 and 11). In such instances, there would be a direct communication between the vasa vasorum and the lumen of the pulmonary artery. It is interesting to note that Short found the vasa opening directly into the lumen of the femoral vein only when there were thrombosis and pathologic changes in the wall of the vein.

In describing the structure of bands and ridges resulting from organized thrombi in the lumen of the pulmonary artery, Saphir noted that many small, newly formed blood vessels were in the wall of the arteries at the point of attachment of these structures to the arterial wall. In the present study, small vessels were also present, extending from the wall into the ridges and bands within the lumen of the pulmonary artery. These vessels were most probably the remains of the vasa vasorum which had grown into organizing pulmonic thrombi.

In an attempt to determine whether branches of the vasa could be traced through the walls of the pulmonary artery in other pathologic conditions, serial sections were made of both normal pulmonary arteries and pulmonary arteries with hypertrophy of the tunica media. In no instances were continuous channels found traversing the thickness of the wall of the pulmonary artery, except in those cases of organizing pulmonary thrombi. Liebow and associates have shown that bronchial vessels enlarge in areas of inflammation or new growth; and since the vasa to the organizing thrombi are branches of the bronchial vessels to such areas, they too do become enlarged. In cases of medial hypertrophy, some of the vasa were enlarged but branches of these vessels could not be traced through the walls of the artery to this hypertrophied tissue. The smaller vasa may be difficult to locate in specimens in which they are not injected, because the inherent elasticity of the pulmonary tissue may so constrict the smaller branches that they are not easily identified within the connective tissue.

Winternitz, Thomas, and LeCompte described the vasa vasorum of the aorta and coronary vessels as arising from three

FIG. 7.

FIG. 7. Section through the wall of a pulmonary artery from a 6 months fetus. Two cross sections through the vasa (indicated by arrows) which coursed in the tunica media are shown. The lumen of this artery is at the top and right, and the tunica externa at the bottom and at the left of this illustration. ×567.

FIG. 8.

FIG. 8. Section through the wall of a pulmonary artery from a 2½ year old male who had an interventricular septal defect. Note part of the endothelial lining (indicated by arrow) of this vessel protruded between cells of the tunica media. ×309.

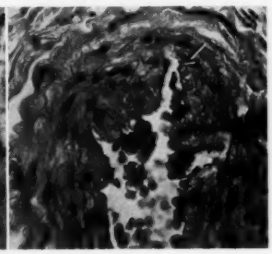

FIG. 9.

FIG. 9. Section through the wall of a pulmonary artery from a 45 year old male who died of cancer of the stomach. Some of the India ink injected into the arterial vasa vasorum was present in the lumen of this artery. Note an outpocketing of the endothelial lining (indicated by arrow) protruding between cells of the tunica intima into the tunica media. ×309.

sources: directly from the lumen of the vessel or from the region of the orifices of its branches—both of these vasa course within the vessel wall. The third type arises from an adjacent vessel and courses within the adventitia for a greater distance than the other branches, on the outer surface of the arterial wall. The present study demonstrates that the pulmonary artery may likewise be supplied: by small channels directly from the lumen (Figs. 8 and 9); by branches which arise from secondary divisions and course within the wall of the artery; and by those which arise mainly from the bronchial artery and travel in the adventitia on the outer surface of the pulmonary artery (Figs. 4 to 6).

The vasa vasorum of the systemic vessels have been reported by Maximow and Bloom to be more abundant on the walls of the veins than on the walls of the arteries, or just the reverse by Lowenberg and Shumacker, more abundant on the walls of the arteries than on those of the veins. Winternitz and associates have also stated in the summary to their book: ". . . In the veins the vasa are exceedingly numerous, and in the pulmonary artery they are easily demonstrated in all coats, though less in number than in the veins . . ." The vasa on vessels in different parts of the body may vary, or the technical procedures used in preparing the specimens may result in blood being forced out of some of the vasa. So as an ancillary part of the present study, portions of the brachial artery and the accompanying veins were removed from the arms of 5 embalmed cadavers and cleared in glycerin. Since the vasa were filled with clotted blood, the artifacts which may be due to handling the vessels were reduced to a minimum. In these studies the vasa were more numerous on the walls of the brachial artery than on the accompanying veins.

In the case of the pulmonary vessels, the more numerous vasa on the pulmonary artery may be due to either the greater thickness of the wall of the artery as compared to that of the veins, or to the relatively smaller amount of oxygenated blood

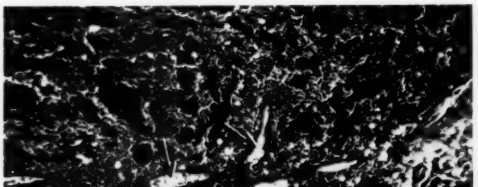


FIG. 10. Section through an organizing thrombus in a branch of the pulmonary artery from a 41 year old male who also had emphysema, cor pulmonale, and pneumonia. Note the size of the vesels (indicated by arrows) within the organizing thrombus. No vessels were traversing the tunica media in this section although there are fairly large branches of the vasa in the adventitia (*AD*). ×157.

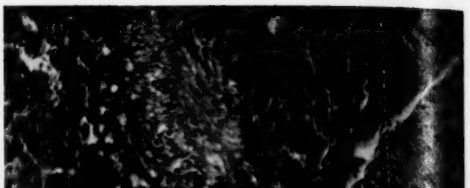

FIG. 11. Another section from the same thrombus shown in Figure 10. Note a vessel cut longitudinally (indicated by arrow) and another vessel cut transversely immediately below it, traversing the tunica media. Followed in serial sections, this vessel arose from the vasa in the adventitia and joined with the vessels within the thrombus. The thrombus is within the sides of the V-shaped fold of this artery. ×157.

carried by the pulmonary artery as compared to the vein. The arterial vasa of the systemic arteries are derivatives of the vessel itself, rather than from another artery. In the case of the pulmonary vessels, the main arterial vasa are derived from the bronchial and not the pulmonary artery. However, like the systemic arteries, small vasa may be derived directly from the lumen of the pulmonary artery or from primary branches of the main pulmonary arterial channel.

The suggestion has also been made that the vasa may serve as collateral channels around an occluded area of the pulmonary artery. It was observed that the vasa were enlarged where they supplied a thrombosed portion of the pulmonary artery. These enlarged vasa may anastomose with adjacent vasa to become the source of collateral channels around the site of obstruction.

## DISCUSSION

The earliest capillary growths into the developing lungs were observed to form the vasa vasorum for the developing pulmonary artery and veins. Studies by Huntington and by Tobin have shown that these early capillary growths are connected to both the pulmonary and bronchial vessels. However, in older embryos those branches developing from the bronchial arteries are the main ones which form the arterial vasa for the pulmonary vessels; whereas the venous vasa are derived from both the bronchial and the pulmonary veins. These early anastomoses between the bronchial and pulmonary vessels remain and may become enlarged and functional in certain diseases of the cardiovascular system.

Most of the emphasis has been given to the pulmonic arterial vasa since the majority of the pathologic changes occur in the pulmonary artery rather than in the veins. These vasa may become enlarged if alterations have occurred in the normal structure of the arterial wall. In addition to this enlargement, in organization of pulmonic thrombi, the vasa were observed to penetrate through the layers of the arterial wall.

The present studies indicate that the branches of the vasa to the adventitia and tunica media usually do not penetrate the internal elastic membrane unless this membrane had been affected by a pathologic process.

One of the main aspects of this problem

centered around whether the pulmonic vasa can penetrate as continuous channels through the entire thickness of the vessel walls. Since both cardiac and striated muscle cells are well supplied with capillaries which are adjacent to the muscle cells and very few tissues of the body have living cells which are located any distance from a capillary, the smooth muscle cells within the walls of the vessels must have some modification of this vascular pattern, although few vessels are usually found in smooth muscle. Caesar and associates and Parker have shown that smooth muscle cells have small vesicles subjacent to their cell membranes which probably represent the passage of substances into or out of the muscle cells. Electron photomicrographs of rat pulmonic vessels (in another ancillary study) also indicate that the smooth muscle cells contain vesicles in the periphery of their borders, which must be related to the metabolic exchange of products for these cells. Perhaps the passage of substances along the connective tissue between the smooth muscle cells represents the smallest vascular channels, which may become enlarged when certain diseases occur in the walls of the vessels and thus result in a continuous channel through the walls of the vessels.

SUMMARY

A restudy of the pulmonic vasa vasorum indicates that these vessels develop from an early embryonic capillary network surrounding the bronchi and pulmonary vessels. This network is derived mainly from the developing bronchial vessels.

Both arterial and venous vasa are present on the walls of the pulmonary artery and pulmonary vein. The pulmonary artery has a richer supply of vasa than a pulmonary vein of comparable size. The vasa may extend as far distally as the pulmonary arterioles and venules. The branches of the arterial vasa normally penetrate to the middle of the tunica media. Outpocketings of endothelium may extend peripherally between cells of the tunica media. The venous vasa of the pulmonary artery empty into the bronchial veins on the adjacent bronchi; whereas the venous vasa on the pulmonary vein enter directly into the lumen of that vessel.

The pulmonic arterial vasa, like other branches of the bronchial artery, become enlarged with the growth of new tissue or if inflammation is present.

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# POTENTIATING INFLUENCE OF APNEA, HYPOXIA, AND HYPERCAPNIA ON BILE-INDUCED HEMORRHAGIC PANCREATIC NECROSIS

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THE ETIOLOGY of acute hemorrhagic pancreatic necrosis remains obscure. Many factors of possible etiologic significance have been advanced. Opie's theory of the common channel lent credence to the injurious properties of bile in the production of hemorrhagic pancreatic necrosis. Trypsin, gastric juice, and hydrochloric acid, injected forcibly into the pancreatic ducts, also produce pancreatic necrosis.

Smyth stressed vascular alterations as the responsible factor in the production of experimental hemorrhagic pancreatitis. Popper, in 1948, clearly demonstrated that acute necrotizing pancreatitis is induced by disruption of the integrity of the pancreatic vascular system. In this work, interstitial pancreatitis uniformly developed when the gland actively secreted against an obstructed ductal system. The lesion could be transformed into severe necrotizing pancreatitis with or without hemorrhage by the addition of temporary occlusion of the arterial system. This report indicates that the production of acute hemorrhagic pancreatic necrosis by the introduction of bile into the pancreatic duct is potentiated considerably by inducing apnea, hypoxia, or hypercapnia.

## METHODS AND MATERIALS

Adult mongrel dogs weighing 6 to 12 kilograms were anesthetized with sodium pentobarbital. Under aseptic technique, the pancreas and duodenum were exposed through a midline abdominal incision. A small polyethylene catheter was inserted into the accessory pancreatic duct—of Santorini—where it entered the duodenal wall. A maximum of 2 cubic centimeters of autologous gallbladder bile was placed within this pancreatic duct at a pressure not exceeding 40 millimeters of mercury, the injection being made over a period of 4 to 5 minutes. The duct was then doubly ligated and transected; the more proximal pancreatic duct—of Wirsung—was not disturbed. Since in the dog, the two ducts are in functional communication, ligation of the duct of Santorini produces only partial obstruction to the outflow of pancreatic juice. The secretion of an enzyme-rich pancreatic juice was stimulated by giving 4.0 milligrams of pilocarpine by the subcutaneous route.

All dogs were intubated with a cuffed endotracheal tube. In pilot experiments, the endotracheal tube was intermittently clamped for periods of time, which varied from 5 minutes at the commencement of the study to 3 minutes toward the close of the experiment. Respiration was permitted for varying intervals (1 to 15 minutes) between episodes of clamping. The total experimental period was 1 hour, with an average of 30 minutes of asphyxia occurring during that time. In this way, a severe degree of intermittent asphyxia was produced (group A—12 dogs).

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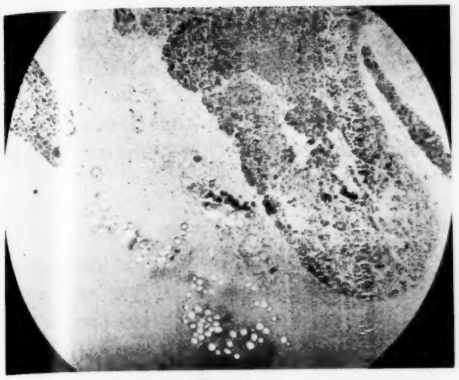
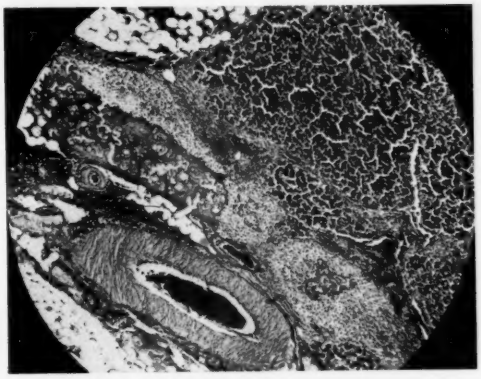


FIG. 1.



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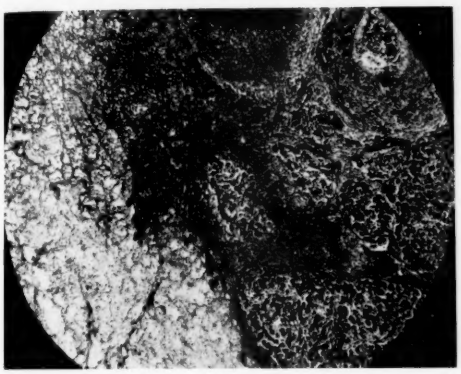

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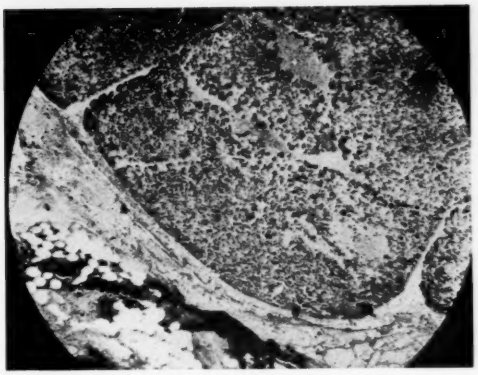

FIG. 4.

FIGS. 1 to 4. Low power photomicrographs of pancreas; hematoxylin and eosin stain. Varying degrees of hemorrhagic pancreatitis with leucocytic infiltration, fat necrosis, and degeneration are shown.

In subsequent investigations, after intubation with a cuffed endotracheal tube, each dog was given sufficient flaxedil to produce apnea. The animals were maintained then on a mechanical respirator, and ventilatory exchange was varied according to the design of the experiment. Again, a total of 30 minutes of asphyxia in a period of 1 hour was accomplished by alternating apneic periods of 5 minutes or less with periods of mechanical respiration. Hypoxia was produced by employing a gas mixture of 84 per cent nitrogen, 6 per cent carbon dioxide, and 10 per cent oxygen in the respirator. Hypercapnia, on the other hand, was achieved by using a gas mixture of 70 per cent oxygen and 30 per cent carbon dioxide. Arterial blood samples were obtained through a cannulated carotid artery.

The animals were divided into five groups. Animals in control group I had no bile placed within the pancreatic duct but did undergo 30 minutes of intermittent asphyxia over a period of 1 hour. Animals in control group II had bile placed within the pancreatic duct at nonduct-rupturing pressure of 40 millimeters of mercury and were curarized by flaxedil, but adequate respiratory exchange was maintained throughout the experiment. Group III, an experimental group, had hypoxia for an hour. At the end of one-half hour, arterial blood samples were analyzed for carbon dioxide content, oxygen saturation, and

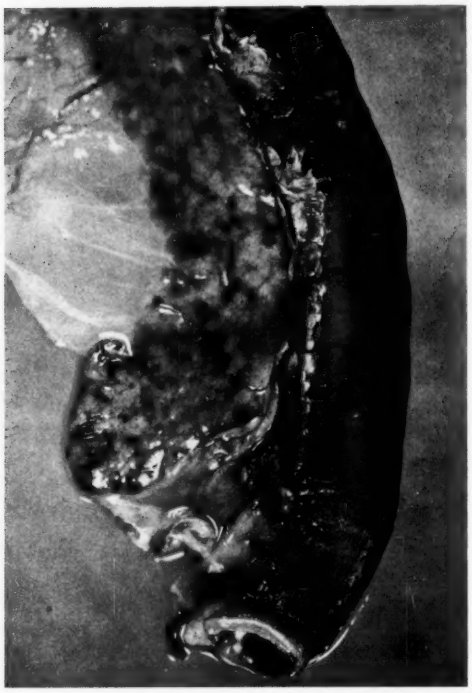

FIG. 5. Epinephrine study of duodenum and pancreas. Note peripancreatic fat, multifocal petechial hemorrhages, and chalky areas of fat necrosis in omentum.

*p*H. Animals in group IV had hypercapnia for 1 hour, and similar arterial samples were obtained at the end of one-half hour. Animals in group V had asphyxia for 30 minutes out of each 1 hour period. Arterial samples were obtained during the second asphyxic period. At the end of each experiment, the animals were maintained on the respirator until spontaneous breathing occurred.

An additional group of 5 dogs (group B) underwent the preliminary preparations of a small amount of bile placed within the partially ligated pancreatic ductal system and pilocarpine stimulation of the gland. However, without altering the breathing of the animals, 1 to 3 milligrams of epinephrine (1:1000) in divided doses were administered intravenously over the hour.

All dogs were returned to their cages. Postmortem examinations, as soon as possible after death, were performed on all animals dying within 48 hours after conclusion of the experiment. Dogs surviving beyond then were sacrificed by the end of 72 hours. Sections of the pancreas were taken and stained with hematoxylin and eosin for further study.

## RESULTS

Three dogs in group A died during the experimental procedure, 1 dog was sacrificed after 48 hours, and 8 dogs died within 24 hours of termination of the experiment (Table I). In all of the latter dogs, 2 or more gross evidences of acute hemorrhagic pancreatitis were present, i.e., hemorrhage into the pancreas, fat necroses, serosanguineous fluid free in the peritoneal cavity and venous thrombi. Histologic examination showed hemorrhage and destruction of the pancreatic cells consistently.

The changes in blood carbon dioxide, oxygen per cent, and *p*H and the accompanying incidence of acute hemorrhagic pancreatic necrosis in dogs of groups I to V are recorded in Table I. The presence of bile in the pancreatic duct or asphyxia alone produced only an indurated nonhemorrhagic pancreatitis. The combination of these two factors succeeded in producing hemorrhagic pancreatic necrosis in almost 100 per cent of the dogs. Hypercapnia or hypoxia associated with bile in the ductal system produced the severe form of pancreatic disease in 50 per cent of the animals.

In group V (asphyxic dogs) microscopic indications of diffuse hemorrhage, acute necrosis of pancreatic cells, and venous thrombi were prominent in all fields viewed. In group IV (dogs undergoing hypercapnia), pancreatic hemorrhage was considerably less and seemed to be mainly confined to the septa between the lobules of pancreatic cells. There were, however, many areas of pancreatic necrosis. In the animals undergoing hypoxia, (group III), hemorrhage did not appear at all prominent, but pancreatic cell necrosis was a frequent finding. In the two control groups,

TABLE I.—EXPERIMENTAL PANCREATIC NECROSIS

| Group | No. of dogs | Experimental procedure | Average blood values: $O_2$ (per cent) | Average blood values: $CO_2$ (mMDL/l) | Average blood values: pH | Time of death | Gross and histologic findings: Hemorrhagic pancreatitis | Gross and histologic findings: Interstitial pancreatitis | Gross and histologic findings: No change |
|---|---|---|---|---|---|---|---|---|---|
| A | 12 | Ligation of pancreatic duct; pilocarpine; asphyxia; bile injection | — | — | — | 3 during operation | 0 | 2 (early) | 1 |
| | | | | | | *1 @ 48 hrs. | 0 | 1 | 0 |
| | | | | | | 8 < 24 hrs. | 8 | 0 | 0 |
| I | 4 | Ligation of pancreatic duct; pilocarpine; no bile injection; asphyxia | — | — | — | *4 @ 24 hrs. | 0 | 4 | 0 |
| II | 4 | Ligation of pancreatic duct; pilocarpine; bile injection; no asphyxia | — | — | — | *4 @ 48 hrs. | 0 | 4 | 0 |
| III | 8 | Ligation of pancreatic duct; pilocarpine; bile injection; hypoxia | 64 | 13.01 | 7.49 | 1 @ 48 hrs. | 0 | 1 | 0 |
| | | | | | | *2 @ 72 hrs. | 0 | 2 | 0 |
| | | | | | | 5 < 24 hrs. | 5 | 0 | 0 |
| IV | 8 | Ligation of pancreatic duct; pilocarpine; bile injection; hypercapnia | 94 | 30.03 | 7.03 | 3 @ 48 hrs. | 0 | 3 | 0 |
| | | | | | | 1 @ 72 hrs. | 0 | 0 | 1 |
| | | | | | | 4 < 24 hrs. | 4 | 0 | 0 |
| V | 7 | Ligation of pancreatic duct; pilocarpine; bile injection; asphyxia | 28 | 25.3 | 7.30 | 7 < 24 hrs. | 6 | 1 (severe) | 0 |
| B | 5 | Ligation of pancreatic duct; pilocarpine; bile injection; epinephrine I.V. | — | — | — | *2 @ 48 hrs. | 0 | 2 | 0 |
| | | | | | | 3 24 hrs. | 3 | 0 | 0 |
| Total | 48 | | | | | | 26 | 20 | 2 |

*Denotes sacrifice.

the picture was that of an edematous gland with good cellular integrity and no hemorrhagic foci.

Of the 5 dogs receiving epinephrine intravenously, 3 dogs demonstrated the gross features of hemorrhagic pancreatitis with a prominence of venous thrombi on microscopic section. Two of the dogs sacrificed at 48 hours showed gross and microscopic interstitial pancreatitis without hemorrhage.

## DISCUSSION

A combination of intraductal injection of bile in an actively secreting pancreas with variations in the composition of the blood produces pancreatic necrosis, whereas either factor alone results only in interstitial pancreatitis. Asphyxia, hypoxia, and hypercapnia all stimulate the sympathetic nervous system and cause release of epinephrine. This may be the common mechanism for the observed effects. Certainly the occurrence of acute pancreatic necrosis after epinephrine administration would tend to support this contention.

A logical sequence could be epinephrine-induced constriction of the pancreatic arterial supply resulting in local ischemia. Increase in the capillary and acinar permeability occurs, and the entire chain of events is accentuated by the secretory activity of the gland, which demands more oxygen and produces more carbon dioxide. There is then intermingling of bile and pancreatic juice with activation of the proteolytic enzymes and destruction of the gland.

The clinical implications of these findings are intriguing. Local vasospasm—during abdominal surgery—and hypoxia or hypercapnia frequently accompany surgical procedures. These situations can be the contributing factor in the genesis of fulminating postsurgical acute pancreatitis in the human.

SUMMARY

Asphyxia, hypoxia, hypercapnia, and intravenous epinephrine definitely augment the damaging effect of bile introduced in the partially obstructed pancreatic duct, resulting in the occurrence of severe hemorrhagic pancreatic necrosis. An underlying physiologic mechanism with epinephrine as the common pathway has been proposed to account for these observations.

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# SOME HEMODYNAMIC EFFECTS OF UREA

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RECENT STUDIES from this laboratory concerning the renal and systemic hemodynamic effects of various intravenously administered substances have prompted us to investigate the influence of urea. This study has seemed important in view of the fact that urea is becoming more commonly used in the management of cerebral and systemic edema.

## MATERIALS AND METHODS

Healthy mongrel dogs were used. They were anesthetized by the intravenous injection of 5 per cent thiopental sodium. An endotracheal tube was passed, and oxygen was administered by means of a mechanical respirator. The mean arterial blood pressure was monitored directly with a U-tube mercury manometer attached to a plastic catheter introduced into a femoral artery. Esophageal temperatures were observed throughout each experiment by means of a telethermometer, and temperatures were maintained at relatively normal levels. Renal blood flow was measured directly by a technique previously described (3). Samples of renal venous blood and of aortic blood were withdrawn and their oxygen saturation was determined by the Roughton-Scholander technique. Total renal oxygen consumption was calculated from the formula:

Renal blood flow in c.c./min. × vol. per cent difference in oxygen saturation between arterial and renal venous blood/100.

The total urine excreted was collected over a 60 minute period from an indwelling catheter. The tubing in the extracorporeal apparatus was siliconized and filled with fresh heparinized dog's blood. Ten milligrams of heparin were given intravenously to each animal prior to the cannulations. The vena caval flows and cardiac input were measured directly by a technique which has been described (9). Blood volumes were calculated from the dilution technique using radioactive iodinated serum albumin. These blood samples were drawn from the inferior vena cava through a femoral catheter.

In 2 groups of 5 dogs each, renal blood flow was measured every 5 minutes during a 15 minute control period and for 60 minutes after the intravenous injection of 1 gram and 1.5 grams of urea per kilogram, respectively. Similar studies were carried out in another group of 5 dogs before, during, and after a 20 minute infusion of 1.5 grams of urea diluted in 50 cubic centimeters of normal saline. During the 5 minutes after the injection or after the beginning of the infusion, the renal blood flow was measured every minute. The volume of urine excreted during the hour after the injection or during the infusion and for a 40 minute period after the infusion was determined. Blood samples for oxygen determination were withdrawn at the end of the control period and at the time when the diuresis usually was found to be at its peak.

In 5 animals the superior vena caval blood flow and in another 5 the inferior vena caval blood flow was measured before and after the injection of 1 gram of urea per kilogram at the same time intervals utilized for studying the renal blood flow. In an additional 14 animals, blood volume studies were carried out. Two control measurements were made 10 and 15 minutes, respectively, after the injection of the radioactive albumin. Measurements were again made

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TABLE I.—URINARY EXCRETION AND CHANGES IN RENAL OXYGEN CONSUMPTION AFTER INTRAVENOUS INJECTION OF 1 GRAM OF UREA PER KILOGRAM

| No. of dog | State of animal | Weight in kgm. | Oxygen content in vols. per cent | | | Renal blood flow in c.c./min. | Renal oxygen consumption | | Urine excretion in c.c. per hour |
|---|---|---|---|---|---|---|---|---|---|
| | | | Arterial | Renal venous | $A\text{-}VO_2$ | Total | Total | Per kgm. body wt. | |
| 1 | Control | 24 | 14.50 | 12.62 | 1.98 | 432 | 7.55 | 0.31 | |
| | Urea | | 12.45 | 9.04 | 3.41 | 384 | 12.99 | 0.50 | 20 |
| 2 | Control | 21 | 18.92 | 18.49 | 0.43 | 546 | 2.35 | 0.11 | |
| | Urea | | 18.32 | 17.37 | 0.95 | 382 | 3.61 | 0.19 | 17 |
| 3 | Control | 15 | 14.60 | 12.48 | 2.02 | 313 | 6.32 | 0.42 | |
| | Urea | | 14.52 | 11.80 | 2.72 | 262 | 7.12 | 0.47 | 14 |
| 4 | Control | 23.4 | 17.28 | 14.21 | 3.07 | 585 | 17.95 | 0.76 | |
| | Urea | | 17.20 | 13.45 | 3.75 | 515 | 19.31 | 0.82 | 22 |
| 5 | Control | 19 | 18.55 | 16.49 | 2.06 | 420 | 8.65 | 0.45 | |
| | Urea | | 16.66 | 12.63 | 4.03 | 298 | 12 | 0.63 | 30 |

TABLE II.—URINARY EXCRETION AND CHANGES IN RENAL OXYGEN CONSUMPTION AFTER THE INTRAVENOUS INJECTION OF 1.5 GRAMS OF UREA PER KILOGRAM

| No. of dog | State of animal | Weight in kgm. | Oxygen content in vols. per cent | | | Renal blood flow in c.c./min. | Renal oxygen consumption | | Urine excretion in c.c. per hour |
|---|---|---|---|---|---|---|---|---|---|
| | | | Arterial | Renal venous | $A\text{-}VO_2$ | Total | Total | Per kgm. body wt. | |
| 6 | Control | 17 | 17.85 | 16.02 | 1.83 | 408 | 7.46 | 0.43 | |
| | Urea | | 16.00 | 7.16 | 8.84 | 374 | 33.06 | 1.94 | 100 |
| 7 | Control | 17.6 | 11.67 | 9.87 | 1.80 | 428 | 7.7 | 0.43 | |
| | Urea | | 10.15 | 7.70 | 2.40 | 337 | 8.1 | 0.46 | 25 |
| 8 | Control | 13.6 | 14.59 | 12.78 | 1.81 | 283 | 5.1 | 0.37 | |
| | Urea | | 15.02 | 12.01 | 3.01 | 250 | 7.5 | 0.55 | 70 |
| 9 | Control | 18 | 16.49 | 16.15 | 0.34 | 400 | 1.36 | 0.07 | |
| | Urea | | 15.13 | 15 | 0.13 | 483 | 0.62 | 0.03 | 80 |
| 10 | Control | 15 | 21.4 | 17.38 | 4.02 | 270 | 10.8 | 0.70 | |
| | Urea | | 20.20 | 14.89 | 5.31 | 291 | 15.45 | 1.03 | 60 |

at intervals during a 90 minute period after the injection of 1 gram of urea per kilogram.

## RESULTS

In the group of animals studied after the injection of 1 gram of urea per kilogram intravenously, a slight decrease in renal blood flow was observed approximately 1 minute after the injection (Fig. 1). By the end of the second minute, the renal blood flow had decreased on the average to approximately 30 per cent below the preinjection level. Simultaneously there occurred a transient decrease in systemic arterial blood pressure. After this initial change, the blood pressure returned to normal. The renal blood flow was then similarly elevated to control values for a period of approximately 10 minutes. After this there appeared to occur a gradual slight decrease in renal blood flow without significant change in blood pressure. The renal oxygen consumption was increased in all 5 animals studied after the injection of urea (Table I). The average preinjection value was 8.56 and the average postinjection value was 11. There was considerable individual variation in renal oxygen consumption that did not appear to be related to the volume of renal blood flow. The urinary excretion after the administration of urea in this group of animals averaged approximately 20 cubic centimeters per hour.

During the first minute after the injection of 1.5 grams of urea per kilogram there occurred an immediate decrease in renal blood flow of about 22 per cent of the control value (Fig. 2). There followed a brief period during which the renal blood flow appeared to be slightly elevated, after which it returned to the preinjection level or slightly below it. Once again the immediate decrease in renal blood flow occurred simul-

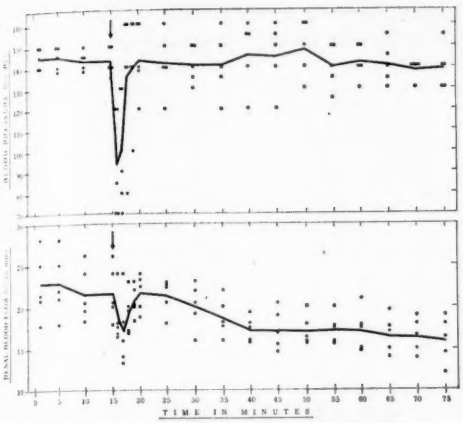


FIG. 1. Response of blood pressure and renal blood flow to the injection of 1 gram of urea per kilogram. The dots represent individual values, the heavy lines the mean values. The arrow indicates the time of injection of the urea.

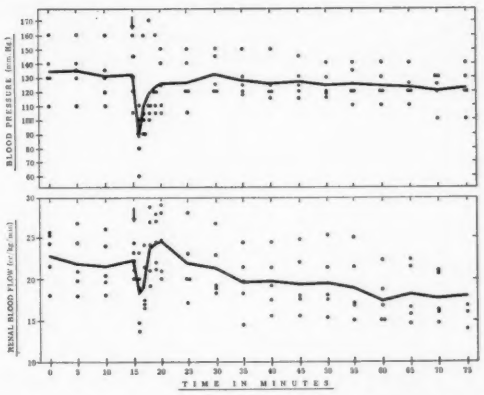


FIG. 2. Response of blood pressure and renal blood flow to the injection of 1.5 grams of urea per kilogram. The dots represent individual values, the heavy lines the mean values. The arrow indicates the time of injection of the urea.

taneously with a fall in systemic arterial blood pressure. In general, renal oxygen consumption tended to increase (Table II). In a single exceptional animal there was some decrease in renal oxygen consumption, however. In 1 animal the increase in oxygen consumption was rather slight. In the other 3 it increased appreciably. One of these had an increase of about 50 per cent in oxygen consumption, and in another the oxygen consumption increased over 4 fold. Urinary excretion in this group of animals was greater than in the first, the average value being 67 cubic centimeters per hour.

The infusion over a 20 minute period of 1.5 grams of urea per kilogram brought about only a very slight decrease in renal blood flow of doubtful significance (Fig. 3). No significant changes in blood pressure were noted. There were no significant alterations in renal oxygen consumption (Table III). In 1 animal, for some unexplained reason, the postinfusion renal venous oxygen saturation was slightly higher than that calculated for the arterial blood. Of the 4 other dogs, there was no essential change in 1, a modest decrease in 2, and some increase in the other. Altogether, there were no consistent changes. The urinary excretion was scant, the average being only 4.4 cubic centimeters during the hour of observation.

The studies of cardiac input revealed a significant, rapid increase in vena caval return during the first few minutes after the injection of urea (Fig. 4). It then decreased rather rapidly and after a short period of time the total cardiac input on the average returned to the preinjection level and remained there during the rest of the period of study. A somewhat different behavior regarding the inferior and superior vena caval components was noted. One minute after the injection of urea the inferior vena caval flow had risen to approximately 30 per cent above the control value. It then tended to decrease gradually but for more than 40 minutes was maintained somewhat above the control value. The superior vena caval flow, on the other hand, increased more markedly immediately after the injection to approximately 60 per cent above the preinjection value. It gradually decreased after 5 minutes to a level approximately 24 per cent greater than the control level and within 20 minutes had returned to the normal level. The pattern of change in vena caval flow in each animal was similar to the mean values for the group. Again a transient pro-

TABLE III.—URINARY EXCRETION AND CHANGES IN RENAL OXYGEN CONSUMPTION DURING THE INFUSION OVER A 20 MINUTE PERIOD OF 1.5 GRAMS OF UREA PER KILOGRAM

| *No. of dog* | *State of animal* | *Weight in kgm.* | *Oxygen content in vols. per cent* | | | *Renal blood flow in c.c./min.* | *Renal oxygen consumption* | | *Urine excretion, c.c.* |
|---|---|---|---|---|---|---|---|---|---|
| | | | *Arterial* | *Renal venous* | *A-$VO_2$* | *Total* | *Total* | *Per kgm. body wt.* | |
| 11 | Control | 16 | 19.29 | 18.51 | 0.78 | 320 | 2.39 | 0.14 | |
| | Urea | | 18.56 | 17.88 | 0.68 | 326 | 2.21 | 0.13 | 2 |
| 12 | Control | 23 | 16.07 | 15.90 | 0.17 | 575 | 0.97 | 0.04 | |
| | Urea | | 15.20 | 15.96 | | 437 | | | 1 |
| 13 | Control | 14 | 17.22 | 13.93 | 3.29 | 252 | 7.29 | 0.51 | |
| | Urea | | 16.45 | 14.25 | 2.20 | 224 | 4.92 | 0.35 | 10 |
| 14 | Control | 21 | 17.28 | 14.21 | 3.07 | 420 | 12.89 | 0.61 | |
| | Urea | | 17.00 | 14.80 | 2.20 | 412 | 9.06 | 0.43 | 4 |
| 15 | Control | 18 | 15.55 | 15 | 0.55 | 491.4 | 1.7 | 0.09 | |
| | Urea | | 15.25 | 14.70 | 0.55 | 505.8 | 2.7 | 0.15 | 5 |

TABLE IV.—BLOOD VOLUME STUDIES BEFORE AND AFTER INJECTION OF 1 GRAM OF UREA PER KILOGRAM

| *No. of dog* | *Wt. in kgm.* | *Blood volume in c.c./kgm.* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *Control period* | | *Time in minutes after injection of urea* | | | | | | |
| | | | | *3* | *10* | *15* | *20* | *30* | *90* | *100* |
| 1 | 15 | 103 | 104 | 103 | 105 | 112 | | | | |
| 2 | 17 | 101 | 104 | 108 | 112 | 102 | | | | |
| 3 | 14.5 | 95 | 113 | 106 | 107 | 116 | 119 | | | |
| 4 | 12.5 | 88 | 108 | 112 | 106 | 120 | 130 | | | |
| 5 | 17.6 | 83 | 110 | | | 121 | 173 | 147 | | |
| 6 | 16 | 96 | 84 | | 95 | 94 | 90 | | | |
| 7 | 14 | 108 | 118 | | | | 134 | 128 | 140 | 173 |
| 8 | 15 | 96 | 110 | | | | 122 | 170 | 140 | 150 |
| 9 | 12 | 94 | 104 | 86 | | | 110 | | 150 | 149 |
| 10 | 11 | 114 | 105 | | 96 | | | | | 142 |
| 11 | 12 | 82 | 98 | | | | 95 | 96 | 95 | 89 |
| 12 | 13 | 82 | 112 | | | | 102 | 100 | 106 | 95 |
| 13 | 11 | 122 | 124 | 134 | | | 152 | 92 | 118 | |
| 14 | 11 | 134 | | | | | 134 | 156 | 138 | |
| Mean | | 99.7 | 107 | 108 | 103 | 110 | 123 | 127 | 126 | 133 |

nounced fall in arterial blood pressure occurred immediately after the injection.

Control estimated values for total blood volume immediately prior to the injection ranged from 84 to 124 cubic centimeters per kilogram (Table IV). The average was 107 cubic centimeters per kilogram, and most of the animals had values approximating the mean. No increase in estimated blood volume was noted in 3 of the animals after the injection of urea and no significant increase in a fourth. All of the rest, however, showed a definite increase in blood volume after the urea was administered.

## DISCUSSION

Our experiments demonstrate that when 1 gram of urea per kilogram of body weight is injected intravenously into the lightly anesthetized, well ventilated, normal, mongrel dog, a diuresis occurs without increase in renal blood flow. A significant, consistent increase in renal oxygen consumption is observed. The arterial blood pressure falls immediately but only momentarily and returns to the preoperative level. During this brief period of hypotension the renal blood flow decreases and then returns to a normal level after which it tends to fall slightly during the remaining period of observation. During the same period when the blood pressure and the renal blood flow fall there is a similarly brief pronounced rise in cardiac output. It then drops rapidly at first and then more slowly and returns to normal within half an hour. The blood volume studies indicate

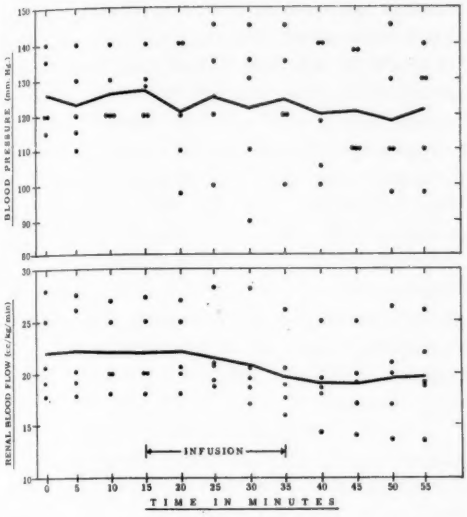


FIG. 3.

FIG. 3. Response of blood pressure and renal blood flow to infusion of 1.5 grams of urea per kilogram. The dots represent individual values, the heavy lines the mean values.

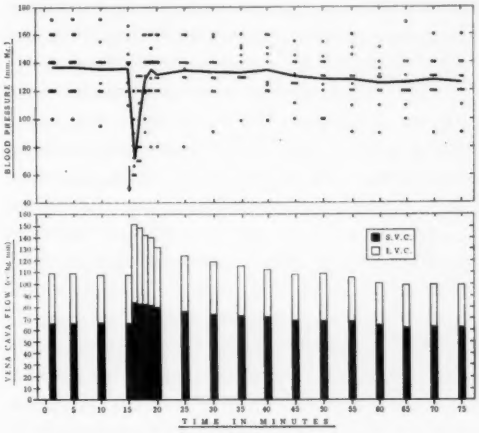


FIG. 4.

FIG. 4. Response of blood pressure and cardiac input to the injection of 1 gram of urea per kilogram. Individual values for pressures are shown as dots, mean values as a heavy line.

that in most instances there occurs a slow rise to a level approximately 30 per cent above normal by the end of 1 hour and 40 minutes.

When a larger amount of urea (1.5 grams per kilogram) is injected intravenously the blood pressure also falls momentarily and then returns to a normal level. The renal blood flow decreases simultaneously but appears to rise momentarily above the pre-injection level at the time that the blood pressure returns to normal. Otherwise the response is similar to that after the administration of 1 gram of urea, the renal blood flow tending to drift downward to a level slightly below normal during the remaining period of observation. Although changes in oxygen consumption of the kidney are more variable, there occurs some increase in oxygen consumption of the kidney in the majority of the animals studied and in some this increase is of considerable magnitude.

The infusion of 1 gram per kilogram of urea over a 20 minute period produces few observable alterations. The blood pressure remains essentially the same. There is only a gradual, very slight decrease in renal blood flow and only a very slight diuresis noted.

The responses of blood pressure and cardiac output to the rapid injection of urea are similar to those observed after the administration of 50 per cent dextrose. The precipitous brief increase in cardiac output is, however, more marked after the administration of dextrose. The injection of both substances produces a diuresis of similar magnitude. There is, however, a striking difference in the effect of the two substances upon renal blood flow. Dextrose produces a pronounced and fairly sustained increase in renal blood flow, whereas no increase, indeed a slight decrease, in renal blood flow follows the administration of urea. Urea also brings about a substantial increase in renal oxygen use.

From the work of Richards and others, it seems well established that glomerular plasma filtration is a simple, passive, physical process, that certain substances are excreted directly by the tubules, and that renal regulation in large measure is dependent upon selective tubular reabsorption of water and solutes from the glomerular filtrate. For the past 20 years the mechanism for the excretion of urea has generally been regarded as a

simple passive process of glomerular filtration and tubular "back diffusion." It has been assumed by most workers that active tubular regulatory or secretory mechanisms are not involved. The fact that the rapid administration of urea in dogs brings about a diuresis and a pronounced increase in renal oxygen consumption without increase in renal blood flow suggests that, in the dog, under these circumstances an active secretory mechanism is involved. The slower administration of the same amount of urea, in contrast, produces only the most minimal increase, if any, in urinary secretion, no increase in renal blood flow, and no consistent changes in renal oxygen consumption. It would, therefore, appear that a substantial and perhaps abrupt rise in blood urea is necessary in order to bring about this active regulatory mechanism.

There are to be found in the literature a number of reports suggesting active tubular secretion of urea in certain animals. In 1932 Marshall found that the amount of urea excreted by the frog's kidney is greatly in excess of the amount which can be accounted for by the glomerular filtrate. He concluded that, in the frog, tubular secretion of urea may occur. An active cellular transport by frog's renal tubules was later observed by Forster. Schmidt-Nielsen (15) found in desert rats that the urea clearance is considerably depressed by excitement and increased by a high protein diet, irrespective of changes in rate of urine flow. Wesson, although claiming that urea reabsorption is a passive process, gave no explanation of the "exaltation" of urea clearance, or the increase observed, which was out of proportion to increasing rates of urine flow. Oyden and Moore showed that more of the filtered urea fails to reach the bladder in the dog under a high water load than in animals under moderate water load and found that an unexpectedly high proportion of the filtered urea failed to be excreted in the urine when the amount of urea filtered exceeded a value of 250 milligrams per minute. They suggested that the tubular epithelium is actively involved in this process when a maximum value of urea filtration is reached. Foldi and Szabo suggested an active tubular secretion of urea in dogs when a 10 per cent urea solution is administered intravenously, since the urea clearance rises and exceeds the glomerular filtration rate. Schmidt-Nielsen and his associates (16, 17) observed in sheep that the renal regulation of the urea excretion is independent of glomerular filtration and plasma urea concentration and therefore concluded that the regulation is on the tubular level, possibly involving an active urea transport.

If urea excretion were regulated on the glomerular level, we should expect changes in glomerular filtration rate and plasma flow parallel with the urea load in the plasma. In our experiments the changes in total renal blood flow were insignificant and only a slight decrease was observed. Some interesting observations in this regard have been reported. Anslow and Wesson observed inconstant changes in renal plasma flow and reduction of glomerular filtration in dogs in which 1 to 5 grams of urea per kilogram were injected. Jolliffe and Smith and Pitts, however, found that a high protein diet in dogs increases considerably the renal plasma flow and glomerular filtration rate, whereas starving has the opposite effect. They therefore concluded that the excretion of urea is somewhat regulated by changes in glomerular filtration rate. Even though the effect of protein load on the renal hemodynamics in dogs still appears to be unsolved, our data demonstrate that no increase in renal blood flow follows the injection of urea. Altogether, the information at hand suggests that the tubule is the site for regulation of urea excretion. The observed increase in renal oxygen consumption would suggest an active aerobic tubular action when a large quantity of urea is given intravenously.

Very few reports have appeared in the literature concerning the cardiovascular hemodynamic consequences of administra-

tion of urea. Gayet-Hallion and his colleagues observed hypotension and vasodilatation after intravenous injections of 0.1 gram of urea per kilogram. A similar result was noted after the injection of solutions of sodium chloride and glucose having the same osmotic pressure. They therefore assumed that the observed hemodynamic effect of urea was due to its osmotic power rather than its biochemical property. Scheinberg observed an increased cerebral blood flow with reduced oxygen consumption in subjects with severe uremia. Incidentally, he observed a marked decrease in mean arterial oxygen content, of unexplained origin, in uremic patients. It is of some interest that in many of our own animals the arterial oxygen saturation was slightly decreased after the injection of urea. We have, as mentioned previously, observed transient hypotension after the injection of other hypertonic solutions. Changes in cardiac input and systemic blood pressure provoked by the administration of urea are similar though less marked than those observed after the administration of concentrated dextrose solutions. Separate study of the superior and the inferior vena caval flow has demonstrated that the superior vena caval flow is affected to a greater degree by hyperosmotic solutions than is that of the inferior vena cava. It would be our belief that the systemic hemodynamic effects of urea are due to the osmotic properties of this crystalloid. We suggested in another article a possible hypothetic explanation of the vascular reaction to the injection of such solutions (2).

It is possible that the administration of hypertonic urea may stimulate hypothalamic osmoreceptors and bring about arteriolar dilatation. This action might tend to increase capillary hydrostatic pressure and would oppose the increased intracapillary osmotic pressure and thus tend to maintain to a certain extent a sort of balance between the two forces regulating fluid exchange through the capillaries. We could, therefore, look upon the fall in systemic arterial pressure as a consequence of response to hypothalamic reflexes occurring as a measure opposing imminent osmotic dehydration of the interstitial space and excessive increase in circulating blood volume. The total cardiac output increases dramatically during the period of observed hypotension. Although one cannot regard the blood volume studies carried out upon these anesthetized dogs as entirely accurate and reflective of momentary changes, no increase in calculated blood volume is observed during the first 10 minute period when these hemodynamic changes take place, but only 20 or 30 minutes later when pressure and flow have returned to normal. It is interesting to speculate that arteriolar dilatation might transmit some of the force from the arterial side through the capillaries and increase the pressure forcing blood back through the venous system. It has been suggested by Burch that arteriolar dilatation accelerates the rate of volume flow into the venous system, producing a slight increase in venous pressure and greater increase in the rate of venous return to the heart. In one of our animals, in which only arterial and venous pressures were measured, we observed a fall in mean arterial pressure from 140 to 80 millimeters of mercury after the injection of urea associated with an increase in the inferior vena caval pressure from 4 to 7 centimeters of water. Because of the distensibility of the venous system, a relatively large increase in venous volume is possible with little change in venous pressure or flow. If venoconstriction were associated with an increased input into the venous collecting system, one would expect an increase in the venous return to the heart and a greater cardiac output.

Whether the experiments reported are applicable to human subjects cannot, of course, be foretold. The fact that the injection of a substantial amount of urea into the blood stream of the dog does not increase renal blood flow but does produce a diuresis associated with an increase, in most instances, of renal oxygen consumption might

make one hesitant to inject a large amount of urea into a patient with marginal or reduced renal function. If our experiments have any pertinence to the problem in human beings, it would appear safe to give urea more slowly as an infusion; but, unfortunately, such an infusion in the dog alters neither renal blood flow nor renal excretion significantly.

SUMMARY

The experiments reported demonstrate that the rapid injection of urea intravenously provokes a transient, abrupt, significant increase in cardiac output associated with a decrease in systemic mean arterial pressure followed by a return of blood pressure to normal levels and a gradual fall in cardiac output. No increase in renal blood flow occurs, a substantial diuresis is noted, and the renal oxygen consumption increases in most animals. The conclusion is reached that under these circumstances urea is excreted by some active process. The slower infusion over a period of time of similar amounts of urea produces no significant hemodynamic effects and no clearcut diuresis. The suggestion is made that until more exact information of this sort is obtained in human beings, it might be considered unwise to utilize urea in patients who have marginal or reduced renal function.

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# A SYNDROME FOLLOWING TOTAL BODY PERFUSION

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INCREASING USE of extracorporeal circulation as a tool in the repair of congenital and acquired cardiac defects has brought to the attention of clinicians a group of postoperative complications not usually seen as sequelae to surgery on other parts of the body nor as a sequel to closed heart surgery. The complications which follow in immediate proximity to the surgery have been well documented. These include, most prominently, metabolic acidosis, atrioventricular conduction defects, and acute heart failure.

There is, however, a group of systemic responses that follows use of extracorporeal circulation, appears with regularity over a period of several weeks after otherwise successful surgery, and is apparently totally unrelated to the primary surgical problem. This study was undertaken to elaborate particularly the hematologic, renal, gastrointestinal, and thermal responses in patients after the use of total body perfusion.

## MATERIAL AND METHODS

Twenty patients undergoing successful open heart surgery constituted the basis of this study. A DeWall type bubble oxygenator was utilized in all cases. The lesions treated included interatrial and interventricular septal defects, atrioventricular canal, aortic stenosis, pulmonic stenosis, and tumor of the right atrium. The youngest patient was 3 years old; the oldest was 37. Except for this latter patient, all others were under the age of 18. Perfusion time varied from 6 to 70 minutes. Cardioplegia was used in 3 cases. The following studies were made:

1. The hematologic status of the patient was assessed in terms of changes in hemoglobin and white blood cell and platelet counts.
2. Changes in renal status were measured by urinalysis which was performed daily for the first 4 postoperative days and then twice weekly for the remainder of the hospital stay. Associated with this test was a parallel measurement of blood urea nitrogen levels.
3. Gastrointestinal changes were measured by a determination of the bowel-sounds, by serial stool guaiac studies, and by barium studies of the gastrointestinal tract in selected patients.
4. Thermal response was determined by rectal temperature readings repeated every 6 hours. In all patients, associated bacteriologic studies were made. These included cultures of blood drawn on at least 2 separate occasions and nose and throat cultures.

## FINDINGS

*Hematologic changes.* Preoperatively, all 20 patients had hemoglobin levels between 12.5 to 15 grams per 100 cubic centimeters. Figure 1 is a composite graph showing mean daily hemoglobin levels. All patients sustained their preoperative hemoglobin levels immediately after operation and on the first 2 postoperative days. Between the third and the fifth postoperative days, 16 of the 20 patients sustained a drop in hemoglobin averaging 3.5 grams per 100 cubic centimeters and to all of these patients blood transfusions were given to restore the hemoglobin to more nearly normal levels. At the time of this first hemoglobin drop none of the patients showed any evidence of intrathoracic bleeding and in none of them was there any significant drainage from the intercostal drainage tubes. All intercostal drainage ap-

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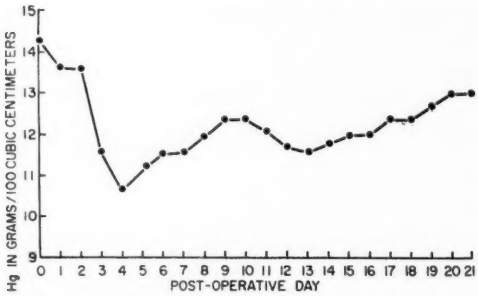


FIG. 1. Variations in average daily hemoglobin levels during the postoperative period.

pearing in the first 48 hours after operation had been replaced volume for volume with whole blood.

A second drop in hemoglobin level was sustained by 15 of the patients between the tenth and the fourteenth postoperative days. This hemoglobin level was restored to normal or near normal levels by the sixteenth postoperative day. In only 3 patients of the series was there any significant drop in hemoglobin beyond the sixteenth day, and in this group only 1 patient required a single transfusion of 250 cubic centimeters of whole blood.

In an attempt to elucidate the cause of this anemia, all patients had serial serum bilirubin determinations performed with each successive drop in hemoglobin of 1 gram per cubic centimeter or more. In only 1 patient, who had a right atrial myxoma, was there a rise in either direct or total serum bilirubin levels at any time in the postoperative period. In this patient a transient jaundice developed on the second postoperative day and cleared completely by the fifth postoperative day. No specific cause was elicited. All remaining patients in the series failed to show any rise in serum bilirubin above normal levels at any time in their postoperative course.

Variations in the white blood cells were studied by serial total white blood cell count and differential counts. Total white blood cell counts are shown graphically in Figure 2. Fourteen patients showed a leucocytosis within 12 hours of completion of the operation, the total white blood cell count averaging 15,000 cells per cubic centimeter in these patients.

In 19 of the 20 patients a marked leucocytosis developed within 48 hours after operation. In all of these patients, white blood cell counts varied between 20,000 and 27,000 cells per cubic centimeter. This marked leucocytosis persisted for 4 days in all patients and then returned slowly to normal. Within 14 days after operation only 8 patients had total white blood cell counts in excess of 10,000 cells per cubic centimeter. Four of these patients had a persistent moderate leucocytosis for a period of 4 weeks after operation.

It should be noted that at the time of maximum leucocytosis in each patient there was only a mild shift to the left in the granulocytic series.

An interesting phenomenon developed in 6 of the patients, namely, the appearance in the peripheral blood smear of atypical lymphocytes very similar to those seen in infectious mononucleosis. The earliest appearance of these cells was in 1 patient who showed such variants within 2 days of operation. The distribution of these cells varied from 2 to 40 per cent of the total white blood cell count. In 4 of these patients these atypical lymphocytes disappeared from the peripheral blood within 21 days after operation. In 1 patient they persisted for 5 weeks, and in 1 patient they persisted for 7 weeks. This latter patient is of special interest, in that he was the only one of the series studied in whom elevation of the heterophil antibody titer and mild splenomegaly subsequently developed. In no other patient did any stigmas of infectious mononucleosis appear.

Platelet counts were made on all patients preoperatively and on the night of and on the day after operation. In no patient in this series was there a drop in platelets below 120,000 per cubic centimeter in any of the determinations.

*Renal changes.* Urinalysis showed that al-

buminuria was present in 20 patients, hematuria in 20, white blood cells in 11, casts in 1, and gross hemoglobinuria in 3.

It is of particular interest that evidence of both albuminuria and microscopic hematuria developed in all these patients within 24 hours of operation. In all but 1 patient, all evidence of these findings had disappeared from the urine between the first and second postoperative week.

The 3 patients who showed evidence of gross hemoglobinuria almost immediately after operation were patients with interatrial septal defects. The longest perfusion time in any of these patients was 20 minutes. Plasma hemoglobin levels determined at the same time as the appearance of the hemoglobinuria were 160 milligrams per cent, 110 milligrams per cent, and 124 milligrams per cent, respectively. The longest duration of the hemoglobinuria was 2 days in 1 patient. It should be noted that in none of these patients was there a rise in plasma hemoglobin levels above that usually considered critical, i.e., 200 to 400 milligrams per cent.

Serial blood urea nitrogen determinations in 19 patients failed to show a rise above 20 milligrams per cent at any time during the postoperative period. In 1 patient only did a serious renal problem develop. This 11 year old boy had an uneventful closure of an interatrial septal defect during 16 minutes of perfusion. From the first postoperative day, the patient showed evidence of a profound renal failure, with marked oliguria and a progressive rise in blood urea nitrogen to a maximum of 168 milligrams per cent on the eighth postoperative day. Between the ninth and the seventeenth postoperative days, the patient had an effective diuresis and his blood urea nitrogen returned to normal levels.

*Gastrointestinal tract.* Postoperative ileus appeared in all patients but was relatively short lived. As determined by the presence of bowel sounds, all patients had a resumption of intestinal peristalsis within 48 hours of operation.

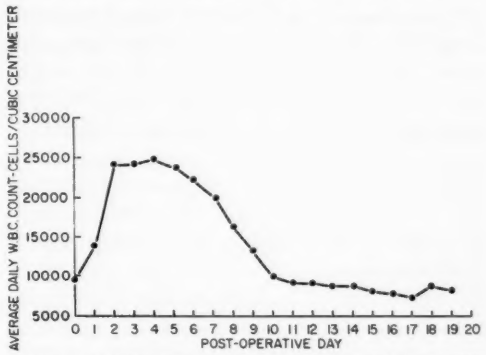


FIG. 2. Variations in average daily total leucocyte count during the postoperative period.

Of particular interest has been the development of gastrointestinal hemorrhage as a complication of extracorporeal circulation. Occult gastrointestinal bleeding shown by guaiac positive stools occurred in 4 patients, tarry stools in 2, and guaiac positive gastric aspirate in 2. There was roentgenographic evidence of duodenal ulcer in 1 patient.

In all cases except 1 the evidence of bleeding did not appear before the third postoperative day, and in none did it persist for more than 7 days. One patient of those who had gastrointestinal tract bleeding showed evidence of a duodenal ulcer deformity on a roentgenogram. In all other cases roentgenographic examination of the gastrointestinal tract was negative.

In none of the patients showing evidence of gastrointestinal bleeding was there an antecedent history of digestive disease.

*Thermal response.* Rectal temperatures were recorded hourly during the first 24 hours after operation, and every 4 hours thereafter. Patients recorded as having fever had a rise in temperature to at least 100 degrees F. at least once during the day.

It was noted that all patients had at least one rise in temperature during the first postoperative day. Eighteen of the 20 patients studied showed a febrile response daily for the first week, and 15 of these patients sustained this daily low grade fever through the second postoperative week.

It is of particular interest that 2 patients who had fever of less than 3 weeks' duration were subsequently readmitted to the hospital within 1 week of discharge because of a recrudescence of fever. Transient lymphocytosis and a palpable spleen developed in both of these patients. No specific therapy was given to 1, and the fever disappeared in 1 week. The other patient had a severe nasopharyngitis upon the second admission. Nose and throat culture at this time grew out Staphylococcus aureus hemolyticus which was sensitive to albamycin. After 3 days of therapy, the fever disappeared. The patient was discharged 10 days after the second admission. In both cases the heterophil antibody titer was not elevated.

It should be noted that a positive blood culture was obtained from none of the patients with fever and that in none was there evidence of significant wound infection. Four of the patients had roentgenographic evidence of patchy areas of pneumonic infiltrates which persisted up to 1 week postoperatively, although in none of these 4 patients was there associated respiratory symptoms such as cough, sputum, or pleuritic chest pain.

## DISCUSSION

A review of clinical and laboratory findings of patients undergoing successful correction of cardiac defects, in which extracorporal circulation techniques were used, reveals an interesting clinical picture.

Evidence of transient anemia will develop in a high proportion of patients during the first and second postoperative weeks. Attempts to establish the cause of this anemia have not been universally successful. In 6 of our patients, the anemia might be explained on the basis of gastrointestinal bleeding, either overt or occult; however, in these cases, the anemia persisted beyond the time when gastrointestinal bleeding stopped (2).

Whether heparinization had anything to do with the gastrointestinal bleeding remains to be seen. All of the patients were titrated with protamine sulfate after the perfusion, and the bleeding and clotting times were normal.

It may be postulated that the drop in hemoglobin represents the result of premature breakdown of red blood cells either because of the marked admixture of the patient's blood with that of multiple donors or because of the mechanical trauma of perfusion. It is surprising that in none of the patients with this anemia was there a marked rise in plasma hemoglobin levels after perfusion and that in only 1 patient was there a significant elevation of serum bilirubin.

The leucocytosis which appeared cannot be explained on the basis of infection, since in very few patients showing this rise of white blood cell count was there any overt evidence of sepsis. The frequent appearance of atypical lymphocytes in the peripheral blood smear is an unusual finding, in that there subsequently developed in only 1 of these patients the elevation of heterophil antibody titer needed to make a certain diagnosis of infectious mononucleosis.

A careful review of the numerous nonspecific responses of patients undergoing total body perfusion for the correction of cardiac defects has caused us to describe this as a postperfusion syndrome. In most patients this will be typified by recurrent anemia, leucocytosis, hematuria, albuminuria, and fever. In a smaller number of patients this syndrome will also include evidence of atypical lymphocytes in the peripheral blood smear and evidence of occult or overt gastrointestinal bleeding.

It is of interest that the clinical picture will clear in most patients within 2 to 3 weeks. In a limited number of patients the clinical picture may persist for 4 to 6 weeks. There are, however, apparently no residual effects of this syndrome. All of our patients in this series have been seen in follow-up clinics over a period of several months after their discharge. In none of the patients were there any residual stigmas of the postperfusion syndrome.

Management of this clinical picture has been empiric:

1. To all patients showing a drop in hemoglobin below 11 grams per cent, blood transfusion was given. These transfusions were independent of those given to replace overt blood loss from intercostal drainage tubes during the immediate postoperative period.

2. Antibiotic coverage was maintained in all patients, beginning the day before operation and continuing for 14 days after operation. After this time, antibiotics were discontinued unless there was any overt source of sepsis. It is interesting to note that the cessation of antibiotic therapy did not elicit any immediate recrudescence of fever in any patient. We have used a combination of penicillin and chloromycetin as the antibiotics of choice.

3. Patients with temperatures above 101 degrees F. were treated with aspirin.

4. Following our early experience with gastrointestinal bleeding after open heart surgery, we have placed all patients on a regimen of frequent small feedings and antacids when oral feedings are resumed. It is worth while to note that we have seen no cases of gastrointestinal tract bleeding since using this regimen.

## SUMMARY AND CONCLUSIONS

A review of the hematologic, renal, gastrointestinal, and thermal responses of patients undergoing successful open heart surgery has been reported.

A postperfusion syndrome including anemia, leucocytosis, hematuria, albuminuria, and fever is reported.

It is noted that in some of these cases this syndrome included the presence of atypical lymphocytes in the peripheral blood smear and gastrointestinal bleeding.

The possible causes of the changes are discussed.

A plan of management for this syndrome is described.

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# PERFUSION OF CHEMICALLY MODIFIED ANTIBODIES FOR THE THERAPY OF CANCER

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WITH INCREASING EVIDENCE of the linkage of virus-like materials to the etiology of human cancer, clinical treatment by active and passive immunization becomes of interest.

In patients with intact reticuloendothelial and lymphoid systems, early in the course of their disease, active immunization is the ideal. Host reactivity can probably be relied upon less and less, however, with degenerative changes in the reticuloendothelial and lymphoid systems. In severely depleted patients, as a result, the emphasis must probably shift to passive immunization.

Tumor antibodies have been prepared and shown to have some therapeutic value by Buinaskas and associates and Murray. Rajam has shown that antibodies chemically modified by insertion of iodine 131 through covalent bonds have increased value. Antibody specificity is known to decrease, however, with the covalent linkage of more than 1 atom of iodine per antibody molecule on an average, as shown by Powell. If only 1 atom or less of cytotoxic moiety can be linked per antibody molecule through covalent bonds, the killing effect on cancer cells will be limited even if the fissionable actinides are linked to antibody for the neutron capture therapy of cancer.

To what extent antigen simplification or development of antigenicity accompanies neoplasia is not known. Wide variation in antigenicity may exist. Because of inherent difficulties in exploiting for therapeutic purposes the potentially small differences in the high polymers of the patient's tumor antigens, however, minimal chemical manipulation of tumor antibodies appears to be desirable. It is possible that alteration of antibody through covalent bonds may be less desirable than linkage of antibody and cytotoxin through weak secondary forms of intermolecular association.

Accordingly, an investigation of colloids of insoluble cytotoxic materials coated with a supporting colloid of antibody is being made, in an effort to increase the amount and variety of toxic material which can be carried to antigen by each antibody molecule and to minimize chemical alteration of antibody molecule in the process.

Tumor tissue does not take up colloidal materials. Previous use of cytotoxic colloids such as chromium phosphate and iron oxide by Lahr and Gilchrist and their associates has resulted in concentration of the cytotoxic colloids in normal tissue or lymph nodes with little going to tumor. The exact reverse is needed for cancer therapy.

By coating cytotoxic colloids with antibody globulin as supporting colloid, or peptizing agent, it is hoped that the cytotoxic colloids can be carried preferentially to antigen. This has been accomplished with uranium (9) and boron (10) colloids for the neutron capture therapy of tumors.

The work on uranium colloids raises the possibility of combining the power of atomic fission with the specificity of antigen-antibody reaction for cancer therapy. More importantly, however, the use of antibody as supporting colloid to bring uranium and boron selectively to antigen may be a general method for effecting concentration of cytotoxic materials in tumors.

If so, many other colloids become potentially valuable. These include the whole

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gamut of radioactive and nonradioactive cytotoxins, such as radioactive gold, silver, palladium, manganese, iron, phosphorus, cobalt, yttrium, and zinc as well as suitably insolubilized antimetabolites, arsenicals, and chelating agents for metallotherapy. Colloids of magnetic materials such as iron oxide for the inductive heating of tumors in an electromagnetic field are also being investigated as well as various combinations of these colloids such as gold or ferrites coated by basic azo dyes containing boron 10 or antimetabolites.

In the past, many colloids have been peptized by use of various proteins or sugars as supporting colloid. Throughout the present work, antibodies are to be used essentially as supporting colloid which coats the underlying cytotoxic colloid in an effort to bring the cytotoxin preferentially to tumor.

Radioactive materials carry the hazard of denaturing antibody by self irradiation. This may be negligible, however, because gold colloids, for example, combine maximally with globulins in 15 minutes as shown by Simon. In addition, the uranium used in our work for preparation of uranium-antibody combinations was deliberately picked for its heavy background of beta and gamma emittors without significant denaturation of antibody after 24 to 48 hours of exposure.

In the choice between radioactive and nonradioactive colloids, the necessity of maintaining a high ratio of tumor dose to whole body dose throughout the entire metabolic cycle of the radioactive material does, however, present serious problems. The use of nonradioactive materials which yield alpha particles or fission products only on exposure to thermal neutrons from an atomic pile, or the use of magnetic colloids such as iron oxide which are heated by exposure to an electromagnetic field, presents the obvious advantages of combining chemical specificity with ability to aim a destructive beam so as to spare normal tissue.

To explore further the possibility of using antibodies as supporting colloids for a variety of cytotoxic colloids, nonradioactive materials have been used in the present work largely because of their availability and ease of handling. The compounds used include antimetabolites, chelating agents, and arsenicals. It was believed that demonstration of preferential localization of colloids from such compounds at the site of antigen after perfusion of the antibody-colloid complexes would suggest the wide applicability of the method.

If chelating agents can be forced to concentrate preferentially at antigen, a second method becomes available for forcing various radioactive isotopes, such as the fissionable actinides, iron, palladium, and cobalt, to concentrate in tumor, in the form of their complexes with the chelating agents. The chelating agents, when given alone, can also withdraw trace metals preferentially from tumors, if colloids of the chelating agents can be forced to concentrate in tumor.

## MATERIALS

The molecules used were designed to accomplish several goals. The resulting colloids were to be red. Sulfonic acid and carboxylic acid groups were avoided since they produce solubility at *p*H 7.4, difficulty in isolating colloids, and a strong tendency to prevent entrance of molecules into cells.

In previous work on the design of the boron-containing colloids, aromatic amine groups were incorporated into the molecules for eventual attraction of the whole molecule to phosphate groups of nucleoproteins to maximize the relative biologic effectiveness of alpha particles released on interaction of boron with thermal neutrons from an atomic pile. Aromatic amine groups were incorporated into the molecules used for the present work, again to maximize toxic effects within cells.

Finally, intense van der Waals forces were thought to be desirable. The difference in free energy of binding of albumin with methyl orange—containing only benzene rings—and with azosulfathiazole—containing also a naphthalene nucleus—is attributed by Klotz and associates largely to the

increased van der Waals forces contributed by the added naphthalene nucleus. Although absorption spectra of dyes do not shift in the presence of gamma globulins as they do in the presence of albumin, it was thought that as a first approximation, naphthalene and quinoline nuclei should give increased binding to globulin by virtue of their increased van der Waals forces and hence should be incorporated into the molecules to be used for the present program.

For the antimetabolites, sulfanilamide, sulfanilanilide, and 4,4′-diaminodiphenylsulfone were diazotized and coupled to N,N-dimethyl-1-naphthylamine to give the 3 corresponding blood red azo dyes. For the chelating agents, sulfanilamide and 4,4′-diaminodiphenylsulfone were diazotized and coupled to 8-hydroxyquinoline to give brown dyes. Because of the poor color, only the first has been used for the present work. Better colors have been obtained with azo dyes containing bis-salicylaldehyde diimines as chelating agents, but they have not yet been converted to colloids. For the arsenical, arsanilic acid was diazotized and coupled to N,N-dimethyl-1-naphthylamine. On perfusion of its colloids, the material appeared to be too soluble so that future work will be done with the corresponding compounds containing -As=O and -As=As- groups in place of the solubilizing $-AsO_3H_2$.

Because permeability of tissue capillaries to colloids and antibodies will be an important factor throughout this program, vasodilators have been investigated. A new series of compounds has been synthesized for metabolic stability, presence of suitable reactive chemical groups, and intense, prolonged activity combined with low toxicity. One of the best for perfusion is N-(4-biphenylyl)-N-(2-diethylaminoethyl) mandelamide, prepared by reaction of acetylmandelyl chloride with the corresponding amine and hydrolysis of the acetyl group. Its activity is about ten times as great and its toxicity less than twice as great as that of procaine. It is a good enough vasodilator to preclude its clinical use as a local anesthetic.

METHODS

The colloids were all prepared by variations of the method to be described for 4-(4-sulfonamidophenylazo)-N,N-dimethyl-1-naphthylamine. After diazotization of sulfanilamide and coupling with N,N-dimethyl-1-naphthylamine, the red dye was filtered, washed thoroughly, and pressed dry. An aliquot of the wet material was used for preparation of the colloid. An amount equivalent to 500 milligrams of the dry dye was dissolved in 40 milliliters of acetone, then admixed with 40 milliliters of 5 per cent aqueous polyvinylpyrrolidone solution. The colloid was then precipitated by rapid addition of 500 milliliters of commercial 6 per cent dextran in saline solution with violent agitation in a colloid blender. The crude colloid was filtered through a standard blood administration set, then centrifuged at 750 × g for 30 minutes. The precipitate was washed with dextran and recentrifuged. The precipitate was then suspended in 30 milliliters of dextran solution and 40,000 units of tetanus antitoxin added. The suspension was blended 3 minutes at high speed with intermittent cooling to hold the temperature below 5 degrees C. The material was then recentrifuged in 12 milliliter heavy duty test tubes at 3,300 revolutions per minute for 30 minutes and the sediment triturated thoroughly with 20,000 units of tetanus antitoxin in a mortar and pestle. The mixture was allowed to stand over night. It was then recentrifuged at 3,300 revolutions per minute for 30 minutes, washed several times with dextran to free the colloid of excess tetanus antitoxin, finally triturated thoroughly in dextran suspension and filtered through a standard blood set before perfusion. All chemical operations involving the antibody were carried out at 0 to 5 degrees C.

The colloids were perfused through the femoral artery and vein in rabbits and dogs according to the method previously described (9). In all cases, a mechanical pump oxygenator small enough to be primed with the animal's own blood was used to avoid

difficulties from vasospasm due to blood incompatibility.

To demonstrate retention of antibody specificity by the antibody coating the colloid, tetanus toxoid was deposited in the lower calf of the animals before perfusion of the antibody complexes. The needle through which antigen was injected was left in place to direct selection of biopsy site. After 45 to 90 minutes of perfusion, multiple biopsies were taken about the needle. By essentially the method of Bratton and Marshall the amount of dye about the site of antigen deposition was compared with that of the rest of the perfused tissue.

## RESULTS

Perfused tissue is similar in color to normal tissue because of the red color of the dyes. As a result, biopsy material from the site of antigen deposition was admixed with much normal tissue containing no antigen, with corresponding depression of the concentration ratios obtained.

Despite this, concentration ratios between 3 to 1 and 12 to 1 were found for dye concentration about the site of antigen deposition relative to that in perfused tissue away from the site of antigen deposition. This was true for all compounds perfused except the arsanilic acid derivative which gave only about a 50 per cent increase of concentration of dye at antigen. The poor result is believed to be due to increased solubility of its colloids conferred by the arsonic acid group so that the compound diffused rapidly throughout the tissue.

The maximum ratio of 12 to 1 was obtained with 4-(4-sulfonamidophenylazo)-N, N-dimethyl-1-naphthylamine, although not in every run. In 1 run in which a maximum ratio of only 3 to 1 was obtained, the dye was seen during perfusion to rise gradually in the needle through which the toxoid had been injected. It is possible that the better results with this compound reflect simply the slight orange tint it gives to tissue so that biopsy can be directed with some accuracy.

Vasodilators used judiciously improved perfusion and localization of the dyes at the site of antigen deposition. The best of these appeared to be a combination of nicotinic acid with an antihistaminic such as 50 milligrams of sodium nicotinate and 10 milligrams of benadryl in a 2 milliliter volume. The use of the antihistaminics was suggested by the action of histamine in raising markedly the pressure in the perfusing system when volume input was held constant by the occlusive Bowman pump used. The action of the antihistaminic reflects probably its activity on large vessels and not at the capillary bed where histamine gives vasodilatation and increased permeability. Various sympatholytic agents and nitrates and nitrites are being investigated for the same purpose.

Local anesthetics such as procaine and N-(4-biphenylyl)-N-(2-diethylaminoethyl) mandelamide also overcame vasospasm effectively and allowed smooth perfusion. Caution must be used with the powerful mandelamide derivative, however. If too high concentrations are used, leakage of the dye-antibody combinations to all the perfused tissues occurs, with corresponding reduction in the ratio of dye concentration at the site of antigen to dye concentration in normal perfused tissue.

Mild hypoxia was also used in this work to increase capillary permeability. In perfusion of the dog's leg, it has been found that low flows of 3 to 10 milliliters per minute give better concentration of colloids at antigen than do higher flows of 30 to 50 milliliters per minute. With high flows and use of large amounts of vasodilator, especially the mandelamide derivative, concentration ratios fell to about 1.5 to 1.

## DISCUSSION

Sulfanilamide, sulfanilanilide, and 4,4′-diaminodiphenylsulfone were selected for initial investigation on this program to serve as models for antimetabolites suitably insolubilized through unstable bonds whose metabolism would release the original antimetabolite to react preferentially with tumor cells. In the case of the sulfanilamide deriv-

atives, these were insolubilized by diazotization and coupling to an aromatic amine with strong van der Waals forces for binding to antibody. The antimetabolite was linked to insolubilizing group through the unstable azo group which can be reduced to primary amine in tissues to release the original sulfonamide, which is an antimetabolite for p-aminobenzoic acid. It is hoped that more toxic antimetabolites can be used similarly.

For that part of the program on beta, gamma emittors, radioiodinated analogues, for example, can be prepared from the red dyes whose colloids have been shown to concentrate at antigen on perfusion of their complexes with antibody. The resulting iodine compounds can then be used in the same way as were the sulfanilamide derivatives to bring the iodine preferentially to antigen. In this way, antibody complexes with radioactive iodine can be formed without the necessity of chemical alteration of antibody through covalent linkage to iodine.

A large number of other organic iodine compounds can also be used to bring radioactive iodine preferentially to antigen. However, they must be capable of being converted to colloids which by virtue of van der Waals forces and other forms of intermolecular association can be bound to the supporting antibody colloid firmly enough to allow their transport by antibody to antigen.

In addition, compounds similar to the red azo dyes described which do combine with antibodies may be used to coat those colloids which do not themselves associate with antibodies so as to produce association of the nonreactive colloid with the antibodies secondarily and hence force concentration of the nonreactive colloid at antigen. In the case of blue or brown colloids, such as some of the gold or ferrite colloids, it may be possible to improve color somewhat by coating them with a thin layer of blood red azo dye possessing strong van der Waals forces for association with antibody.

Although antibodies used as supporting colloid for a variety of cytotoxins appear to be able to force concentration at antigen of such cytotoxins, it is not intended that such antibody complexes be used alone for the treatment of cancer patients. They can be supplemented in several ways.

If early in the course of his disease, the patient appears capable of forming his own antibodies, these should be used to supplement standard forms of therapy. Autogenous vaccines can be prepared by the method of the Grahams using adjuvants to increase response. Vasodilators going preferentially to tumor and iodine 131 substituted antibodies may enhance the effects obtained by active immunization and are being investigated for this purpose. Agents which stimulate the reticuloendothelial system may also be useful to supplement the program on active immunization in patients with a reticuloendothelial system capable of responding.

In addition, tumors are chemically vulnerable in two other ways independent of adult metabolic functions which might be lost with increasing anaplasia. As a result, two classes of compounds are to be used to supplement the effects of the antibody complexes, the first going preferentially to the central part of tumors, the second going preferentially to the periphery of tumors where tumor is actively invading host.

As Stevens and associates have indicated, at the central portion of tumors, glucose administration especially after a period of starvation, produces a drop in *p*H to allow preferential concentration of weak acids, such as sulfanilamides, when these are injected as their salts. A boron substituted sulfanilamide has been prepared, therefore, to supplement the program on antibody complexes of boron colloids. Other antimetabolites and cytotoxins containing weak acid groups, such as sulfonamide derivatives of mapharsen and radioiodinated organic amines can be used to supplement the action of various antibody complexes.

In addition, this drop in *p*H at the central portion of tumors may allow preferential activity there of compounds such as triethylene melamine reacting by a bimolecular nucleophilic substitution mechanism whose

reactions are catalyzed by acid, according to Ross. Such compounds should also be used to supplement the activity of antibody-colloid complexes, the alkylating agent preferably being perfused rather than injected parenterally. Because such alkylating agents damage the reticuloendothelial and lymphoid systems it is possible that they should be reserved for those patients whose reticuloendothelial and lymphoid response has already been damaged by cancer and who are being treated by passive immunization. Correspondingly, it is possible that the alkylating agents should be withheld during early stages of the disease when attempts are being made to capitalize on the patient's own defenses through active immunization.

At the periphery of tumors, polar anionic compounds are known to reach high concentrations. Boron substituted Evans blue, according to Kruger, reaches ratios of up to 100 to 1 in depolymerized ground substance at the periphery of brain tumors, relative to that in normal brain. With boron and other cytotoxic moieties which must react within cells, such polar anionic derivatives will lack therapeutic effects because the polar anionic groups responsible for bringing the compound to depolymerized ground substance will also prevent entrance of the molecule into the cell. One method to solve the problem for cytotoxins which must react within cells is to link them to polar anionic groups by bonds which are metabolically unstable. Linkage of cytotoxic groups such as arsenic, boron, or antimetabolite to polar anionic groups by metabolically unstable bonds, such as those of aldehyde bisulfite adducts or aldimine sulfonic acid derivatives, may allow concentration of the whole molecule at the periphery of tumor, metabolic removal of polar groups, and finally entry of the cytotoxic moiety into cells.

Aldehyde bisulfite adducts—such as those from pyruvic aldehyde, crotonaldehyde, and glyoxal—and Schiff bases—from salicylaldehyde sulfonic acid—have been prepared from: various sulfanilamides; 4,4′-diaminodiphenylsulfone; boron and iodine substituted sulfanilamides; mapharsen; aromatic amines, diamines, aminophenols and hydrazines; and iodinated aromatic amines. These have been perfused in dogs and rabbits without difficulty. Alone or in combination, after intravenous injection of 10 to 20 per cent of their median lethal dose, these caused varying inhibition without cure of a transplanted mammary adenocarcinoma in Strong A mice, in our laboratories.

For cytotoxic groups such as boron or antimetabolite which must act within cells, this type of unstable polar derivative will be used to supplement the program on colloid-antibody complexes. Compounds of the fissionable actinides or the beta, gamma emittors, by contrast, may contain 1 or more sulfonic acid groups or 2 or more carboxylic acid groups preventing their entry into cells because the range of action of their irradiation exceeds the diameter of cells. Thus, radioiodinated compounds, for example, can also be designed to contain stable linkage to 1 or more polar groups for concentration in depolymerized ground substance to add to the program on antibody-colloid complexes.

For any antibody-colloid complex found suitable for use, the basic steps to be followed for clinical application will be the same. Portions or extracts of the patient's tumor cells, or the patient's fibrin will be used as antigen by the method of Day and associates. If etiologic nucleoproteins are found for the cancer, these will be used as antigen. If inadequate quantities of antigen are available, tumor cells will be grown in a cytogenerator following Graff's procedure or a medullary growth will be harvested by heterotransplantation of the patient's tumor into guinea pigs' eyes by the method of Greene, for example. Resulting antigen, from extraction or breakup of the tumor cells, will be injected into horses, sheep, or preferably lactating cows and antibody collected. If antigen changes during treatment, new antibodies must be made. The antibodies then will be made to react with suitable cytotoxic colloids and the resulting complex injected parenterally or perfused

in the patient, along with various supplementary agents, discussed before.

If boron 10 colloids or colloids of the fissionable actinides are of value, the patient will finally be exposed to a beam of thermal neutrons from an atomic pile. If magnetic colloids for inductive heating of tumors are of value, the patient will finally be exposed to a radiofrequency generator. If radioactive colloids as of gold, phosphorus, or iodine, or nonradioactive colloids from cytotoxins as arsenic or antimetabolites are used, no further exposure of the patient will be needed.

Permeability of tissue capillaries to complexes of colloids with antibodies will be a constant problem throughout this program. When the present artificial test system is discarded and tumor antibody complexes are finally tested against tumor, a more logical way to increase the permeability of capillaries of the tumor will be available. Vasodilators such as tertiary amines, nitrates, and nitrites themselves can then be modified by the chemical methods enumerated before to achieve preferential localization in tumors.

The powerful vasodilator, N-(4-biphenylyl)-N-(2-diethylaminoethyl)-mandelamide, was deliberately chosen for perfusion because of the presence of the alpha hydroxyl group. This group permits the formation of esters of marked instability. These can contain weak acids for concentration at the central portion of tumors or sulfonic acid groups for concentration at the periphery of tumors. By insertion of amine groups on the aromatic nuclei unstable adducts containing sulfonic acid groups may also be formed for concentration at the periphery of tumors. As with the cytotoxic compounds, the directing groups can be metabolized off, to release the vasodilator for preferential activity in tumors.

Such vasodilators should be used to increase capillary permeability of tumors both during early therapy with autogenous vaccines as well as in the later stages of the disease, when emphasis has shifted to passive immunization and use of complexes of various cytotoxic colloids with supporting colloids of antibodies against tumor.

SUMMARY

Colloids do not concentrate in tumors but are taken up preferentially by normal tissue. The reverse is needed for cancer therapy. It has been demonstrated that antibodies can be used as supporting colloids for a variety of cytotoxic colloids without loss of antibody specificity. As a result, it should be possible to bring many radioactive and nonradioactive cytotoxic materials preferentially to tumor by use of their complexes with antibodies against tumor.

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# EXPERIMENTAL STUDIES ON THE RELATION BETWEEN ACCELERATION AND INTRACRANIAL PRESSURE CHANGES IN MAN

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THE PROBLEMS primarily investigated in the present studies are: (a) whether or not the body weight augmented the impact of the head against an automobile instrument panel, i.e., whether the fact that the body was attached to the head produced a more severe impact to the head than if the head alone were dropped on the instrument panel as in our previous investigations (1); (b) the relationship between acceleration and intracranial pressure produced when the head struck a thin steel plate, an automobile instrument panel, and a large steel block; (c) the time duration of the pressures and accelerations occurring during impact of the head; and (d) the probable intracranial pressure and its time duration accompanying concussion. The data obtained from the tests may also be of use to the automotive design engineer in developing safer automobiles.

## MATERIALS AND METHODS

*Material.* The material used in the study consisted of 4 embalmed, white, male cadavers of human beings who had died of cholecystitis, pneumonia, carcinoma of the pancreas, and an unknown cause at ages 64 to 76 years. Twenty-three individual tests (drops) were made, divided into 5 series of different types. Each body was weighed before testing.

*Testing apparatus.* In order to determine the effect produced by the mass of the trunk of the body when the head is decelerated (negative acceleration) by contact with an automobile instrument panel or other object, a special apparatus was constructed. The apparatus (Fig. 1) consisted of a framework of aluminum channels attached to a massive cast iron base plate by means of two ball-bearing pillow blocks. This arrangement allowed the framework to rotate freely in a vertical plane.

The cadaver was supported at the axillae in an upright position within the frame and was securely fastened in place by web belts. The frame with the cadaver in place was permitted to fall by free rotation about the base. If a higher velocity was required, the initial force of a push was applied to the frame while in the vertical position. Thus, control of the motion of the body was provided while allowing the head only to strike the target object. In all tests, the impact was applied to the forehead of the cadaver.

*Preparation of the cadaver for testing.* Intracranial pressure changes occurring during a test were measured by means of pressure transducers with a capacity of 300 pounds per square inch mounted in the right temporal and the left posterior parietal regions of the head. In order to mount the transducers, circular pieces 1 to 1.5 inches in diameter were cut from the scalp to expose the underlying bone. Holes were then drilled through the skull in the prepared areas and tapped to receive the transducers.

Before mounting the transducers, part of the brain was removed to gain free access to the ventricles of the brain and avoid trapping air in them. The brain tissue was re-

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moved by a vacuum pump attached to a copper tube introduced into the cranial cavity through the holes for the pressure gauges. Care was taken to insure that the falx cerebri and other meningeal structures were thoroughly punctured and torn so that all parts of the cranial cavity communicated with one another.

After enough of the brain was removed to provide access to the ventricles, the cranial cavity was filled with fluid gelatin and the head was packed in ice to promote setting of the gelatin. The ice was removed just before testing. During a test it was assumed that the mechanical behavior of the gelatin, in the transmission of intracranial pressures, would be similar to that of the brain and other skull contents.

Before the pressure gauges were screwed into the skull, a thin rubber gasket was slipped over the threaded end of the gauge and thickly coated with F-88 dental cement. This procedure provided a good solid seat between the gauge and the skull, as the cement hardened in a few minutes.

The acceleration during a test was measured with a 1,000 g capacity Statham accelerometer mounted on the occiput of the cadaver's head. For this purpose a circular piece of the scalp, large enough to accommodate the accelerometer, was cut from the occipital region so that the accelerometer was in contact with the skull. During a test, the accelerometer was held in place with straps passing around the head. In order to prevent embalming fluid from leaking into the areas where the pressure gauges and accelerometer were mounted, the edges of the incisions through the scalp were tightly sewed with overlapping sutures and the seams coated with celloidin.

*Recording instrumentation.* The pressure gauges and the accelerometer were connected to different channels of an oscilloscope equipped with a camera, so that a permanent record could be obtained. At the time of impact, high speed motion pictures, 1,500 or 2,000 frames per second, were taken.

Preliminary tests were made to determine the response of the pressure gauges to acceleration. For this purpose, the gauges were attached to a fixture which was permitted to drop from different distances onto a padded surface so as to obtain a range of acceleration values. The hydraulic connection to the gauges was not made for these tests, since the effects of acceleration alone on the gauge output signal was to be determined in these studies.

The results obtained from the tests indicated that the effect of acceleration on the pressure pickup output depended on the direction of orientation of the pickup axis with respect to the direction of acceleration. It was determined that when the pickup axis was perpendicular to the direction of acceleration, the effect of the latter on the output was negligible. For this reason, care was taken to mount the pressure pickups in the skull so that they would be at right angles to the direction of the blow.

*Test procedure.* The cadaver, firmly strapped into the frame of the testing apparatus, was permitted to fall freely, rotation occurring about a horizontal axis at the bottom of the frame. The distance from the axis of rotation to the point of impact on the forehead of the cadaver was measured for each test. The average distance was 68 inches. Generally, the first drop of each test series was onto an automobile instrument panel which was struck at a point just above the glove compartment door. The second drop in a test series was made onto a flat steel plate 12 by 36 inches by 0.036 inch thick clamped at the edges. The third drop in a series was made onto a solid steel block weighing 160 pounds. For these drops, the body and frame were held in such a position as to bring the head within 36 inches of the steel block before being released. In order to evaluate padding material in terms of reduced intracranial pressure produced in the head, tests were made in which polyurethane pads, 3 inches thick, were placed over the metal surfaces. The material of these pads was similar to the padding material used in the standard production instrument panel.

RESULTS OF THE TESTS

*First test series.* The first test series of 5 drops was made with the body of a white male 76 years of age whose legs were amputated at the proximal third of the thigh.

In the first drop the head struck a flat, 12 by 36 inch thin steel plate 0.036 inch thick, clamped at the edges. The recorded intracranial pressure in the temporal region was 22 pounds per square inch, and in the parietal region it was −9 pounds per square inch, with a duration of 0.007 second. The velocity of impact was 15 miles per hour, but the acceleration was not determined.

The second drop was made under the same experimental conditions. In this test the intracranial pressures recorded were 25 pounds per square inch for the temporal region, and −7 pounds per square inch for the parietal region. Duration of the blow was 0.008 second. The measured acceleration was −125 g (g=32.2 ft. per sq. sec.), with the same velocity used in the first drop. The results of the first two drops were very similar.

For drop 3, a polyurethane pad 3 inches thick was placed over the steel plate and the test was repeated with all other factors remaining unchanged. Because of the pad, the magnitudes of the acceleration and temporal pressure were reduced to −84 g and 12 pounds per square inch, respectively, but the time duration was increased to 0.016 second. Thus, although the pressure was reduced by a factor of 2, the time duration was increased by the same factor. The parietal pressure was not obtained.

In drop 4, a polyurethane pad 3 inches thick was placed on the 160 pound steel block. The measured acceleration for the drop was −69 g, the temporal pressure was 16 pounds per square inch, and the parietal pressure was 6 pounds per square inch. The time duration of the blow was 0.012 second.

Negative pressures recorded in the parietal region apparently arise from the deformation of the skull which bends outward in this region. This phenomenon was verified by high speed motion pictures taken in previous tests. A positive pressure in the parietal region indicates that the skull deformation was markedly reduced by the pad inserted between the head and the steel block. As in the previous test, the time duration of the blow was increased by use of the pad.

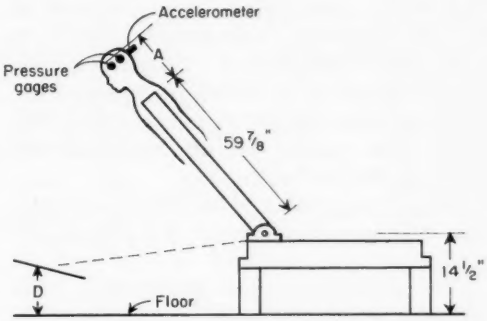


FIG. 1. Apparatus used for applying impact to forehead of intact human cadaver. *D*=distance.

The fifth and last drop of the first test series was made with the head striking the bare steel block after falling a distance of 3 feet. This drop produced an acceleration of −237 g, a temporal pressure of 32 pounds per square inch, and a parietal pressure of −15 pounds per square inch, lasting 0.006 second. A slightly depressed comminuted fracture was produced. These results are not directly comparable with those obtained in the preceding drop, since the velocity of impact for drop 4 was 15 miles per hour, whereas in drop 5 it was only 10.9 miles per hour. However, a comparison of the results indicates the great advantage of using the pad. The high negative pressure in this drop shows the large deformation occurring in the skull in the parietal region. If fracture had not occurred, both the acceleration and pressure would have reached higher values.

*Second test series.* The second series of tests was made with the body of a white male 69 years of age. The legs were amputated in the proximal third of the thigh, and the pressure gauges and accelerometer were attached in the same positions as those in the first series of tests.

Drop 6 was made on a 1956 automobile

instrument panel with an impact velocity of 15 miles per hour. This drop resulted in a measured acceleration of −43 g and a temporal pressure of 15 pounds per square inch. The duration of the pressure was 0.015 second. No reading was obtained from the gauge in the parietal region.

Drop 7 was similar to the preceding drop, and only temporal pressure of 8 pounds per square inch was obtained.

The eighth drop was made on a 1954 automobile instrument panel. An acceleration of −85 g and a temporal pressure of 16 pounds per square inch lasting for 0.008 second were recorded. The parietal gauge failed to record. Because of the stiffer section of this panel, the increase in acceleration and pressure over that obtained for the 1956 panel is logical. Comparing the results of drops 7 through 9 with drops 1 and 2 indicates a proper trend. Accelerations and pressures are greater for the flat panel with clamped edges, as was to be expected.

Roentgenograms of the head indicated that no fractures were produced by the drops in the second series of tests.

*Third test series.* Since the body used in the second series of tests was undamaged, it was used again in the third series of tests. Drop 9, the first in this series, was made on a 1956 automobile instrument panel at a velocity of 15 miles per hour and an acceleration of −48 g. A temporal pressure of 14 pounds per square inch was produced and lasted for 0.016 second. No parietal pressure reading was obtained. This reading constitutes an excellent check on the values obtained in drop 6 in which all the conditions were the same.

In the tenth drop, the 1956 panel was covered with a standard production pad which resulted in an acceleration of −43 g, a temporal pressure of 9 pounds per square inch, and a parietal pressure of 3 pounds per square inch with a time duration of 0.02 second. These results indicate slight reductions in acceleration and pressure and an apparent decrease in skull deformation because of the pad over the instrument panel.

Drop 11 was made on the flat plate with clamped edges. The recorded acceleration was −104 g and the parietal pressure −14.5 pounds per square inch. The duration of the impact was 0.005 second, considerably shorter than that resulting from impact on the instrument panel. The temporal pressure was not recorded.

Drop 12 was on the heavy steel block through a distance of 3 feet. The recorded acceleration was −43 g lasting 0.005 second. No pressure readings were obtained. The acceleration reading is obviously too low and the result was discarded as no test. A linear fracture of the skull was produced.

*Fourth test series.* The fourth series of tests was made with the completely intact body of a 64 year old white male.

Drop 13 was made onto a 1956 automobile instrument panel with a striking velocity of 15 miles per hour. An acceleration of −48 g, a temporal pressure of 7 pounds per square inch, and a parietal pressure of −3 pounds per square inch, lasting for 0.005 second, were recorded. The results are quite similar to those obtained in drops 6 and 9 made under similar test conditions. However, a shorter time duration of the impact existed in the present test.

In drop 14, the head again struck a 1956 automobile instrument panel, but the body was given an initial push, thus increasing the velocity of impact. This additional force resulted in a somewhat higher acceleration of −70 g, but the temporal pressure was the same, and the parietal pressure increased to 6 pounds per square inch. The duration of impact was also increased to 0.008 second.

Drop 15 was made on the flat steel plate with clamped edges, and an acceleration of −171 g was recorded, with a parietal pressure of −10 pounds per square inch lasting 0.002 second. The body was thrown forward to increase the impact velocity. The results of the test compare quite well with drop 11 made under similar conditions, with the exception of a velocity of impact reduced to 15 miles per hour.

Drop 16 was a repetition of drop 15 to the

flat plate, with the exception that the body was permitted to fall freely, thus obtaining a striking velocity of 15 miles per hour as in drop 11. The measured acceleration was −159 g, the parietal pressure −7 pounds per square inch, and the temporal pressure 19 pounds per square inch. The duration of impact was 0.008 second. The results conform reasonably well with those of drop 15.

In drop 17, the body was dropped on the heavy steel block through a distance of 3 feet. A recorded acceleration of −176 g, a parietal pressure of −15 pounds per square inch, and a temporal pressure of 42 pounds per square inch, with a duration of impact of 0.006 second were recorded. There was no fracture. The results appear to be of the same order of magnitude as those obtained in drop 5 made under similar test conditions.

*Fifth test series.* The fifth series of tests was conducted with the intact body of a 71 year old white male.

Drop 18 was made on a 1956 automobile instrument panel with an impact velocity of 15 miles per hour. This drop resulted in an acceleration of −63 g, a parietal pressure of −2 pounds per square inch, and a temporal pressure of 5 pounds per square inch. The duration of the blow was 0.022 second.

Drop 19 was made on a 1954 automobile instrument panel, using the same impact velocity as in the preceding drop. The recorded acceleration was −65 g, the parietal pressure −6 pounds per square inch, the temporal pressure was 6 pounds per square inch, and the duration of the blow was 0.016 second. The magnitudes of acceleration and pressure showed a slight increase over those obtained using a 1956 automobile instrument panel.

In drop 20 the body was thrown forward to give a slightly increased impact velocity to the head striking a 1956 automobile instrument panel. The results obtained, however, did not reflect the added impact velocity, since the acceleration was only −57 g, the temporal pressure 3 pounds per square inch, and the time duration 0.009 second. The parietal pressure was not obtained.

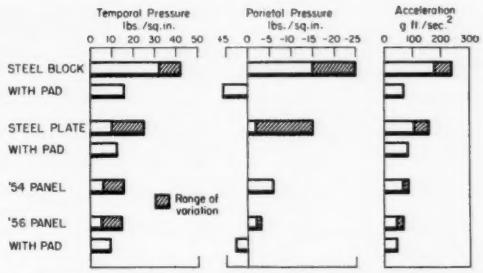


FIG. 2. Average and range of variation in intracranial pressures and accelerations in human cadaver heads according to various impact surfaces.

In drop 21, made upon a 1954 automobile instrument panel, the body also was thrown forward so that a slight increase in acceleration of −74 g was obtained. This was accompanied, however, by a decreased temporal pressure of 1 pound per square inch. Duration of the impact was again 0.009 second, and parietal pressure was not obtained.

In drop 22, the head struck the flat steel plate at a velocity of 15 miles per hour. A recorded acceleration of −113 g, a parietal pressure of −2 pounds per square inch, a temporal pressure of 10 pounds per square inch, and an impact duration of 0.009 second were obtained. The pressures recorded were considerably lower than those found with other bodies subjected to similar test conditions.

The final drop, 23, was made on the steel block through a distance of 3 feet. This produced an acceleration of −85 g, and a temporal pressure of 5 pounds per square inch lasting for 0.008 second. The parietal pressure was not obtained. The acceleration and pressure were both quite low in comparison with similar tests of other bodies. No fracture resulted from the test. The factual data obtained in the tests described are summarized in Table I.

## DISCUSSION

Previously unpublished tests in which intact cadaver heads were dropped through

TABLE I.—SUMMARY OF TEST RESULTS

| *Test No.* | *Drop No.* | *Acceleration, g's* | *Temporal pressure* | *Parietal pressure* | *Time, seconds* | *Impact velocity, m.p.h.* | *Impact surface* |
|---|---|---|---|---|---|---|---|
| 1 | 1 | — | 22 | −9 | 0.007 | 15 | Flat steel plate, clamped edges |
| | 2 | −125 | 25 | −7 | 0.008 | 15 | Flat steel plate, clamped edges |
| | 3 | −84 | 12 | — | 0.016 | 14.5 | 3 in. thick pad on flat steel plate |
| | 4 | −69 | 16 | 6 | 0.012 | 15 | 3 in. thick pad on steel block |
| | 5 | −237 | 32 | −25 | 0.006 | 10.9 | Steel block, 3 foot drop |
| 2 | 6 | −43 | 15 | — | 0.015 | 15 | 1956 automobile instrument panel |
| | 7 | — | 8 | — | 0.008 | 15 | 1956 automobile instrument panel |
| | 8 | −86 | 16 | — | 0.008 | 15 | 1954 automobile instrument panel |
| 3 | 9 | −48 | 14 | — | 0.016 | 15 | 1956 automobile instrument panel |
| | 10 | −43 | 9 | 3 | 0.020 | 15 | Production pad on 1956 panel |
| | 11 | −104 | — | −15 | 0.005 | 15 | Flat steel plate, clamped edges |
| | 12 | −43 | — | — | 0.005 | 10.9 | Steel block, 3 foot drop |
| 4 | 13 | −48 | 7 | −3 | 0.005 | 15 | 1956 automobile instrument panel |
| | 14 | −70 | 7 | 6 | 0.008 | 15+ | 1956 automobile instrument panel, body given initial velocity |
| | 15 | −171 | — | −10 | 0.002 | 15+ | Flat steel plate, body given initial velocity |
| | 16 | −159 | 19 | −7 | 0.008 | 15 | Flat steel plate, clamped edges |
| | 17 | −176 | 42 | −15 | 0.006 | 10.9 | Steel block, 3 foot drop |
| 5 | 18 | −63 | 5 | −2 | 0.022 | 15 | 1956 automobile instrument panel |
| | 19 | −65 | 6 | −6 | 0.016 | 15 | 1954 automobile instrument panel |
| | 20 | −57 | 3 | — | 0.009 | 15+ | 1956 automobile instrument panel, body given initial velocity |
| | 21 | −74 | 1 | — | 0.009 | 15+ | 1954 automobile instrument panel, body given initial velocity |
| | 22 | −113 | 10 | −2 | 0.009 | 15 | Flat steel plate, clamped edges |
| | 23 | −85 | 5 | — | 0.008 | 10.9 | Steel block, 3 foot drop |

TABLE II.—IMPACT TESTS WITH INTACT CADAVER HEADS DROPPED UPON A 160 POUND STEEL BLOCK 3 INCHES THICK

| *Cadaver Age, race, sex, cause of death* | *Head weight, lbs.* | *Distance dropped, inches* | *Impact energy, lbs.* | *Impact velocity, m.p.h.* | *Accel., g* | *Duration of acceleration, sec.* | *Remarks* |
|---|---|---|---|---|---|---|---|
| 83 W M Pneumonitis | 9.25 | 54 | 500 | 11.6 | −456 | 0.001 | No fracture |
| — | — | 65 | 618 | 12.5 | −557 (peak) −180 (avg.) | 0.002 | Linear fracture |
| 78 W M Myocardial infarction | 6.81 | 71.5 | 487 | 13.4 | −372 | 0.002 | Fracture |
| 71 W M Cerebrovascular thrombosis | 10.44 | 60 | 626 | 12.2 | −460 | 0.001 | Fracture |

distances of 54 to 80 inches are available for comparison with the results of the present investigation. In these studies, as in some of the present ones, the head was dropped on the 160 pound steel block. In each test the head was caught on the rebound so that it struck the steel block just once. In the previous studies eight tests were made, using 6 heads. In these tests 2 heads failed to fracture when dropped through a distance of 54 and 60 inches, respectively. Simple fractures determined by roentgenogram were obtained after drops of 60, 65, 70, and 80 inches. Accelerations only were measured in these tests and the total energy of impact was determined from the weight of the head and the distance dropped.

The results of 4 of these earlier tests (Table II) will be described. In the first test a 9.25 pound head from a white male 83 years of age was dropped from a distance of 54 inches, providing an impact energy of 500 inch pounds and an impact velocity of 11.6 miles per hour. The blow produced an

acceleration of −456 g lasting 0.001 second but no fracture.

A second test was made with the same head using a drop of 65 inches and an energy of 618 inch pounds. The impact velocity was 12.5 miles per hour. Although peak acceleration of −557 g was reached, the average acceleration was only −180 g with a duration of 0.002 second. A linear fracture was produced.

In the third test the head of a white male, 78 years of age was used. This head which weighed 6.81 pounds was dropped through a distance of 71.5 inches, producing an impact energy of 487 inch pounds and an impact velocity of 13.4 miles per hour. The blow resulted in an acceleration of −372 g with a duration of 0.002 second and a fracture.

The head of a white male, 71 years of age was used in the fourth test. This head, the heaviest of the four, 10.44 pounds, was dropped from a distance of 60 inches, giving an impact velocity of 12.2 miles per hour and an impact energy of 626 inch pounds. An acceleration of −460 g lasting for 0.001 second was recorded. A fracture was produced.

In the present investigations 2 fractures were obtained in 4 tests when the intact body was dropped through a distance of 36 inches upon the 160 pound steel block. Direct comparison of these results with the earlier ones can be made only between tests in which the head struck the same solid steel block. In both series of tests it was assumed that under the tests' conditions the amount of available kinetic energy absorbed by the steel block was negligible. Consequently, all or nearly all of the available kinetic energy of a test was expended in deforming or fracturing the head. This means there was little, if any, energy transferred between the head and the steel block. The accelerations in the present series of tests (−176 g to 237 g) were less than those obtained when the heads alone were dropped (−370 g to −456 g), as in the earlier tests, but the duration of the blow was about 3 times as long. Thus, a comparison of the present results with those of the previous investigations definitely indicates that the mass of the body adds to the severity of the blow to the head. Roentgenograms taken after testing failed to disclose any fractures or dislocations in the cervical spine.

TABLE III.—SUMMARY OF TEST RESULTS

| *Impact surface* | *Acceleration, g* | *Parietal pressure, lb./sq. in.* | *Temporal pressure, lb./sq. in.* | *Time duration, sec.* |
|---|---|---|---|---|
| Steel block, 3 foot drop Impact velocity, 10.9 m.p.h. | 176 to 237 | −15 to −25 | 32 to 41 | 0.006 |
| Flat steel plate, Clamped edges Impact velocity 15 m.p.h. | 104 to 159 | −1 to −15 | 10 to 25 | 0.005 to 0.010 |
| 1954 automobile instrument panel Impact velocity 15 m.p.h. | 65 to 86 | −6 | 6 to 16 | 0.008 to 0.016 |
| 1956 automobile instrument panel Impact velocity 15 m.p.h. | 43 to 63 | −3 to −2 | 5 to 15 | 0.005 to 0.012 |
| 3 inch thick pad on flat plate Impact velocity 15 m.p.h. | 84 | — | 12 | 0.016 |
| 3 inch thick pad on steel block Impact velocity 15 m.p.h. | 70 | 6 | 16 | 0.012 |
| Padded 1956 panel Impact velocity 15 m.p.h. | 43 | 3 | 9 | 0.022 |
| Same panel unpadded | 48 | — | 14 | 0.016 |

In the other tests (Table I) in which the head struck an automobile instrument panel or the flat steel plate with or without a pad, a considerable amount of the available kinetic energy was transferred from the head to the impact surface and was expended in denting the impact surface rather than deforming or fracturing the head. The relation of the different impact surfaces to the range of variation in acceleration, parietal and temporal pressure, and time duration of the blow are summarized in Table III.

Examination of Table III and Figure 2, in which the results of the present series of drops are graphically presented, reveals a

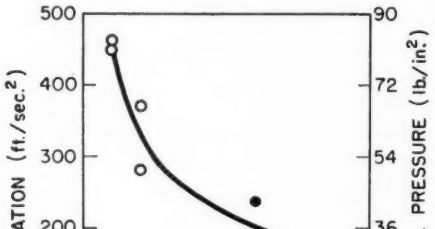


FIG. 3. Relation between acceleration and time required to produce fracture in heads falling freely and in heads falling with the body attached.

decreasing severity of the blow from the steel block to the 1956 automobile instrument panel. The results also demonstrate that the 1956 instrument panel is an improvement over the 1954 one, in that there is a reduction in the acceleration and the parietal pressure produced. The latter indicates that the skull deforms less as the panel tends to warp or bend around the head.

In most of the present series of tests a positive pressure was produced in the temporal region and a negative pressure in the parietal region. In only 2 instances, one with the padded steel block and the other with the padded 1956 instrument panel, was a positive parietal pressure recorded (Fig. 2). The temporal pressure gauge was located about 2 inches behind the forehead and the parietal gauge about 2.5 to 3 inches further back. The negative pressure in the parietal region results from the deformation of the skull. When the impact occurs, the region receiving the blow bends inward, causing the parietal bones to bend outward, producing a region of reduced pressure in this area. The pressure immediately under the point of the blow would, of course, be higher than that recorded in the temporal region. However, since straight line pressure distribution from the parietal to the temporal region is extremely unlikely, the magnitude of this pressure cannot be computed.

Previous studies of experimental concussion (4) have shown that the damage occurs primarily in the brain stem in the region of the foramen magnum. In closed head injuries (5) the concentrated damage in the brain stem is the result of pressure gradients between the general cranial cavity and the junction with the spinal cord. It has also been shown (2, 3) that concussion can occur from acceleration, deceleration, or compression as the result of an increase in intracranial pressure at the time of impact. With compression, the increase in intracranial pressure is more uniform throughout. However, acceleration and deceleration injuries result in intracranial pressure increases with pressure gradients in the cranial cavity. Gurdjian and associates (2) have also emphasized that the time duration of the pressure and of the acceleration are of equal significance with the magnitude of the acceleration and of the pressure. Thus, the shorter the time duration of acceleration or pressure the higher the pressure necessary to produce a concussive effect. The longer the time duration the lower the pressure may be in order to effect a concussion. The magnitude of the pressure within the brain in the critical area just above the foramen magnum cannot be determined, since the gradient existing across the head is unknown.

Any padding arrangement or reduction in stiffness of the panel or both which increases the time duration of impact in an equal or diminished ratio to the decrease in acceleration or pressure produced will be an improvement with regard to prevention of injury. With regard to the increased time duration of the blow when using a pad to reduce the acceleration and pressure, previous tests on dogs described by Gurdjian, Webster, and Lissner (4) have shown that the relation between pressure and the time required to produce concussion is not a straight line as illustrated in Figure 3 of that article.

That the same kind of condition exists for human beings as is required for the reduction of concussion in dogs appears to follow from the time-acceleration relationship required to produce fracture in human heads (Fig. 3). Although much more data must be obtained before valid conclusions can be drawn, the information thus far available indicates that the same physical damage results from reduced acceleration and from pressure if the time duration is increased. Thus, when the heads alone were dropped, a higher acceleration and shorter time duration were required to produce a simple fracture than in the case in which the heads were dropped with the body attached. Of course fracture and concussion are entirely different, but since the heads struck the same surface—the 160 pound steel block—in both series of tests, producing the same sort of a simple skull fracture, it is reasonable to assume that the same type of brain concussion might result from both blows.

The temporal pressure produced by the 3 foot drop of the head, with body attached, ranged from 32 to 42 pounds per square inch and lasted 0.006 second. This condition produced linear fracture and presumably resulted in cerebral concussion also. If we assume a direct ratio between acceleration and pressure for impact on the steel block, the pressures produced in the heads dropped from 4.5 to 6 feet would range from 50 to 81 pounds per square inch with a time duration varying from 0.001 to 0.002 second.

SUMMARY

1. Twenty-three drops, divided into 5 series of tests, were made with the embalmed bodies of 4 adult white male cadavers. The apparatus and instrumentation, as well as the method of making the drops, are described and illustrated.

2. In the first 3 series of tests, constituting drops 1 through 12, the legs of the cadaver were amputated in the proximal third of the thigh. In the remaining series of tests and drops, the intact body was used. In all test series, the blow was applied to the forehead of the cadaver. The impact surfaces were a 160 pound 3 inch thick steel block, a flat steel plate clamped to the edges, the same plate covered with various types of padding, a 1954 automobile instrument panel, and a 1956 instrument panel.

3. The velocities in the tests were 10.9 miles per hour and 15 miles per hour. The accelerations produced during a test were measured by an accelerometer attached to the occiput. Intracranial pressures in the parietal and temporal regions were measured by pressure transducers. The duration of the pressure was measured in seconds.

4. A 3 foot drop on the 160 pound steel block produced an impact velocity of 10.9 miles per hour and an acceleration varying from 136 to 237 g. The parietal pressure varied from −15 to −25 pounds per square inch, and the temporal pressure from 32 to 42 pounds per square inch. The average time duration of the pressure was 0.006 second. The reason that the pressure gauges registered greater negative values than the standard atmosphere gauge pressure at absolute zero (−14.696 lbs. per sq. in.) was because of the adhesion between the cranial contents and the metallic diaphragm of the pressure gauges.

5. When the body was dropped on a flat steel plate with clamped edges with an impact velocity of 15 miles per hour, the acceleration varied from 104 to 159 g, the parietal pressure from −2 to −15 pounds per square inch, the temporal pressure from 10 to 25 pounds per square inch, and the duration of the pressure from 0.005 to 0.010 second.

6. Use of a 1954 automobile instrument panel with an impact velocity of 15 miles per hour produced a variation of from 65 to 86 g in acceleration, a parietal pressure of −6 pounds per square inch, and a temporal pressure of 6 to 16 pounds per square inch. The duration of the pressure was 0.008 to 0.016 second.

7. Similar tests on a 1956 automobile instrument panel reduced acceleration from 43 to 63 g, the parietal pressure from −3 to

−2 pounds per square inch, the temporal pressure from 5 to 15 pounds per square inch, and the duration of the pressure from 0.005 to 0.022 second.

8. When a polyurethane pad, 3 inches thick, was used on a flat plate with an impact velocity of 15 miles per hour, an acceleration of 84 g and a temporal pressure of 12 pounds per square inch, with a duration of 0.016 second were obtained. The same velocity when the head struck another polyurethane pad on the steel block resulted in acceleration of 70 g, a parietal pressure of 6 pounds per square inch, and a temporal pressure of 16 pounds per square inch. The duration of the pressure was 0.012 second.

9. When a padded 1956 instrument panel was used with an impact velocity of 15 miles per hour, the acceleration amounted to 43 g, the parietal pressure 3 pounds per square inch, and the temporal pressure 9 pounds per square inch. The duration of the pressure was 0.022 second. Another test on the same panel, when unpadded, resulted in an acceleration of 48 g, and a temporal pressure of 14 pounds per square inch, with a duration of 0.016 second.

10. A slightly depressed comminuted fracture was produced in drop 5 in the first series of tests and a linear fracture of the skull in drop 12 in the third series of tests. The first fracture resulted when the head struck the solid steel block after falling through a distance of 3 feet, with an acceleration of −237 g, a temporal pressure of 32 pounds per square inch, and a parietal pressure of −15 pounds per square inch, lasting for 0.006 second. The impact velocity was 10.9 miles per hour. The linear fracture was produced by dropping the head on the same block with the same impact velocity.

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# TOTAL SPHINCTEROPLASTY WITHOUT DRAINAGE OF THE COMMON BILE DUCT IN THE TREATMENT OF BILIARY TRACT DISEASE

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THE PATHOLOGIC ROLE of the sphincter of Oddi has been known for a long time but it has aroused only intermittent interest among surgeons. If both the pathology of tumors, which is now well known, and the functional pathology, which has still not been very well explained since it is often intricately associated with the pathology of lesions, are disregarded, two important groups of surgical works in contemporary literature remain, those of Cattell which have shown the determining role of the sphincter of Oddi in postcholecystectomy syndromes and those of Doubilet which have established the role of the sphincter of Oddi in pancreatic colic. During the last few years, the junction of the common and pancreatic ducts has been shown to be a key area for a large proportion of hepatobiliary and pancreatic pathologic conditions.

It has become apparent in the light of numerous histologic, anatomic, and radiomanometric findings that this natural constriction at the junction of the common and pancreatic ducts, which forms a highly sensitive contractile sleeve, is a favorite area for major inflammatory involvement of the common bile duct. The crux of the problem of treatment often lies in the narrow passage formed by the sphincter of Oddi since any impairment of this passage hinders the free flow of bile. If this problem is to be solved, two essential and basic technical questions must first be considered in detail: (1) What surgical procedure should be used for treating the sphincter? (2) How can an impairment of the sphincter be diagnosed with certainty? In our opinion these two questions can be answered as follows: (1) total sphincteroplasty and (2) the use of pharmacodynamic radiomanometry.

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## SPHINCTEROPLASTY

The very term "sphincteroplasty" is open to criticism for, rather than representing a true plastic operation, the operation in question consists of a triangular resection the length of which takes in the whole of the duodenal side of the sphincter. Common usage has, however, made this term generally accepted and we have accordingly retained it.

We have performed this operation in more than 100 cases during the last 3 years. For us, it involves four clearly defined principles.

1. The sphincteroplasty should be total. The bile must be allowed to flow freely by means of a veritable mutilation which should be made without any recourse to drainage of the common bile duct and should establish a wide open communication between the common duct and the duodenum. In this way, the sphincteroplasty will prevent all relapses of the stenosis in any part of the sphincter that has been left in place, and a final and lasting cure will be obtained.

This total sphincteroplasty has long been a source of apprehension on account of the risk of a contingent ascending cholangiolitis provoked by the duodenal reflux. Such fears are without foundation. Transpapillary drainage, by permitting duodenal reflux, brings an end to cholangiolitis, in the opinion of all investigators who have used it. Above all, our experience with choledocho-

FIG. 1. Reflux after sphincteroplasty. The long term results are good; there has been no cholangiolitis due to reflux.

duodenostomy has shown us, as well as others whose experience with this procedure runs to several hundred cases, that this operation is absolutely free from all danger even though it produces a far larger reflux than that obtained after a total section of the sphincter. It is not the duodenal reflux that provokes cholangiolitis but stasis and the difficulty of re-establishing the normal flow of the bile. Many cases of cholangiolitis reported after an anastomosis between the biliary and digestive tracts or after a sphincterotomy can be ascribed to a secondary stenosis resulting from faulty surgery.

2. The sphincterotomy should not be accompanied by drainage of the common bile duct. Such drainage serves no useful purpose if the technique allows a perfect choledochoduodenal mucomucosal suture to be made and ensures that the whole of the common duct anastomosis remains wide open.

3. The sphincterotomy should not be accompanied by choledochotomy. There is no need for any mutilation of the common bile duct which can, in fact, only do harm. Thanks to systematic peroperative radiomanometry, it is quite possible for a lesion of the sphincter of Oddi to be diagnosed without any recourse to instrumental exploration. The sphincterotomy is therefore a strictly duodenal procedure.

4. Cholecystectomy must be performed systematically. Total sphincterotomy, while permitting the reflux, also allows stasis to occur in the gallbladder diverticulum, thus provoking inflammation. Since the gallbladder diverticulum has, moreover, lost its point of support on the sphincter of Oddi, it no longer fills and no longer plays any physiologic role.

*Technique.* In order to facilitate the approach to the papilla, it is essential that the duodenum and pancreas be separated. This is a bloodless maneuver and can be carried out easily and rapidly. Even in the case of obese subjects, it exposes the operative field as far as the cutaneous incision plane.

The exact limits of the duodenotomy area are established by transparietal palpation by means of a semirigid rubber bougie with a diameter of 2 millimeters introduced into the cystic duct. It will usually go through the papilla but, should it be prevented from passing by a tightly constricted odditis or an embedded calculus, the tip of the bougie will press on the papillary region and enable it to be identified. The duodenotomy should be performed exactly opposite the papilla between two support points 2 centimeters apart. The incision should be made lengthwise and be 15 millimeters long. It should be at the same distance from the mesenteric insertion. A lengthwise incision causes no more hemorrhage than a crosswise one. Access to the operative field is assured by two retractors. A pull on the intraduodenal bougie enables the papilla to be located; it is then harpooned with a fine needle fitted in a holder and can thus be easily exposed.

The rubber bougie is gradually removed and replaced by a fine grooved probe which catheterizes the papilla, the constricted pas-

sage through the sphincter of Oddi, and then the common bile duct. This catheterization is generally easy to perform, even when the sphincter of Oddi shows a marked sclerosis since, once the tip has passed under the papilla, the probe can be forced through. There is one danger, however: the probe is often liable to go into Wirsung's duct more easily than into the common bile duct. It should be guided in such a way as to ensure that, as it moves forward, the tip rests against the upper wall of the sphincter of Oddi constriction, and the common bile duct should be palpated to make sure that the probe really has gone into it. This mistake is very easy to make at first, with the result that the probe penetrates very superficially into the pancreas for a distance of 6 centimeters, i.e., as far as the isthmus.

The groove in the probe allows two needles threaded to either end of a piece of catgut to be guided to the point where it is desired to limit the sphincteroplasty, i.e., at least 15 millimeters so as to ensure that the section will take in the whole of the extramural choledochal sphincter. A pull on these two needles will show the distal support point of the sphincteroplasty.

The papillary opening is transfixed with two diametrically opposed stitches made with No. 00 catgut applied to the mucosa and the common sphincter. These represent the two proximal support points which, with the previous one, mark out the triangle to be resected.

The triangle is resected with the aid of fine, tapered Martel scissors with curved ends. The incision toward the apex of the resection may be extended if necessary, but this extension should be done gradually so as to make sure that the pancreas is not affected. This section is generally bloodless. When the papilla is badly inflamed, any troublesome secretion can be stopped by dabbing with serum to which epinephrine has been added. If a small vessel spouts blood, it can be compressed witha fine clamp, final hemostasis being obtained when the choledochoduodenal suture is made.

FIG. 2. Numerous stones are present in the common bile duct. The extraction of calculi via the duodenal route after sphincteroplasty is easier and more complete than after a choledochotomy.

Forceps are inserted into the gaping opening and the two limbs opened out to give the size of the opening which corresponds to the retropancreatic portion of the common bile duct.

The opening of Wirsung's duct is located systematically; the duct can always be catheterized quite easily with the aid of a stylet.

The three points of the triangle are stretched apart, and the duodenal mucosa is carefully sutured to the wall of the common bile duct with 8 to 10 stitches of No. 00 catgut. The prior locating of the opening of Wirsung's duct ensures that it will not be choked by one of the suture stitches. Once the sphincteroplasty has been completed, any stones that may be present can easily be extracted via this route with the aid of long fine instruments, such as Randall-Mirizzi forceps, Del Valle curets, or a Van

FIG. 3. Lithiasis of the common bile duct and narrowing of the inferior common bile duct by pancreatitis. The most effective procedure is choledochoduodenostomy.

Tornouth scraper. The duodenotomy is closed on two planes by overcast Liganyl seams following the direction of the incision. The length of the opening is so small that a closure using separate stitches made crosswise cannot be considered.

The abdomen is closed without draining, except in the case of an uncontrollable welling out of blood in the dissection area or from the gallbladder bed when a latex drain leading out through a short counteropening made by a right subcostal incision, aspirated if need be, will suffice if left in 3 to 4 days.

## RADIOMANOMETRY

The basic essential of all biliary tract surgery is correct peroperative exploration of the biliary tract. In this, radiomanometry holds a place of the highest importance

Radiomanometry, described in France, represents enormous progress in the appreciation of the organic and organofunctional pathology of the sphincter. Two main techniques were described at an interval of 1 year. That of Mallet-Guy, described in 1944, separates the cholangiographic and manometric investigations and, with the aid of an air manometer connected to a recording drum, makes a graphic recording of the stabilization of the pressure after a hyperpressure of 40 to 60 centimeters of water has been provoked. That of Caroli, described in 1945, combines the cholangiographic and manometric investigations with the aid of an apparatus enabling constant perfusion pressures to be obtained.

Since 1957, after using these two types of radiomanometric exploration in turn for several years, we have used a new method involving a simpler apparatus and providing results that are more truly physiologic.

*Technique.* The complexities involved in the initial application of the two standard methods, the inconveniences resulting from the use of apparatus that cannot be handled directly by the surgeon, the relative inaccuracy of the zero level, the irritation of the sphincter occasioned by extraphysiologic fluids or fluids injected at pressures that are too high and thus provoke defensive spasms of the sphincter, and the highly artificial nature of the so-called "residual" figure obtained after an induced hyperpressure have led us to abandon the two methods discussed as much as we appreciate their merits.

Instead, a simple manometric study is made that is separate from the cholangiographic investigation and to which are added two pharmacodynamic tests of great interest. During the first phase, consisting of the manometric investigation, after the cholecystectomy has been performed and a polythene tube introduced into the cystic duct, a glass tube, 3 millimeters in diameter, 30 centimeters long, and tapered at one end, is fitted directly into the polythene tube and held vertically. The height of the bile reflux

into the tube is measured in centimeters from the level of the common bile duct which gives a direct reading of the pressure in centimeters of bile in accordance with the hydrostatic principle that the pressure exerted at a point for a given density is equal to the height of the column of liquid.

In order to induce an active physiologic choleresis during the test similar to that which occurs in the course of meals, 100 milligrams of sodium dehydrocholate are injected intravenously 5 to 10 minutes before the examination, this being the time required for the salt to produce its effect. This choleresis is induced without affecting the tonicity of the sphincter of Oddi. It is accompanied by an increased mobility of the common bile duct and constitutes a truly physiologic test since no changes are provoked in the highly sensitive functioning of the sphincter by any foreign fluid that might cause a greater or lesser degree of irritation, the temperature of which is more or less variable, and which is injected from the outside at a relatively high pressure. The test is strictly accurate and involves no risk of error in the evaluation of the pressures. It is a dynamic functional test which assesses the flow pressure, i.e., the physiologic synergism between the hepatic secretion and the sphincter of Oddi, and shows whether the bile flow is likely to pass through the papilla at a normal pressure of 10 to 12 centimeters during the digestive process.

In contrast with this, the "residual" pressure measured by the other radiomanometric techniques, i.e., the stabilization pressure in the common bile duct after the provoking of a slight or marked hyperpressure, in a hepatic duct system that is at rest is indeed an arbitrary figure. The pressures recorded with our method have been proved correct, in spite of laparotomy and anesthesia without premedication liable to exert an action on the smooth muscles, the apnea required for the taking of roentgenograms having been obtained by hyperoxygenation.

Normally, the flow pressure varies between 10 and 12 centimeters; occasionally

FIG. 4. Stenosis of a long section of the common channel in the region of the sphincter of Oddi with pancreatitis provoked by reflux in the Wirsung and Santorini ducts.

reduced pressures of 6 or 7 centimeters are observed. A pressure of 16 centimeters or more indicates that the bile is being hindered in its passage through the sphincter of Oddi. However, before the existence of an obstacle is confirmed, a cross-check is absolutely essential; this is provided by the amyl nitrite spasmolytic test. This involves simply the breaking of an ampule of this volatile product into the anesthetic circuit. Whenever the flow pressure reaches or exceeds 16 centimeters, any pre-existing spontaneous or provoked spasm will yield spectacularly and consistently within 20 to 30 seconds.

If carried out systematically in biliary tract surgery, this simplified method of manometry will, when supported by the sodium dehydrocholate induced choleresis test and the amyl nitrite spasmolytic test, enable each sphincter to be investigated with great precision.

The results of this manometric procedure should always be compared with the cholangiographic test which is carried out during the second stage. The fine manometric

FIG. 5. Numerous small stones in the region of the sphincter of Oddi. It is not certain that they have all been extracted. Sphincteroplasty permits the elimination of any that may have been overlooked.

tube is replaced by a pipette with a diameter of 1 centimeter which is fitted in the same way into the transcystic polythene tube so as to ensure a tight fit. An average of 6 roentgenograms are taken at different pressures, acediodone (a tri-iodized hydrosoluble product) being injected through the opening at the top of the tube. Thus an exact picture is provided of the junction of the common bile duct and the duodenum, which is seldom characteristic of odditis, and any obstacles are revealed that may be impeding the bile flow, in particular stones in the common duct.

The whole of the radiomanometric exploration usually does not take more than 15 minutes. With the additional data provided by the pharmacodynamic tests, the manometric and radiologic studies make instrumental exploration obsolete since, if the latter were used alone, it would often lead to glaring errors. Unless a systematic use is made of radiomanometry, there will continue to be cholecystectomy sequelae, excessive resorting to sphincterotomies, unnecessary choledochotomies, and a number of postoperative disasters.

## INDICATIONS FOR SPHINCTEROPLASTY

*Lesions of the sphincter of Oddi without accompanying lithiasis in the common bile duct.* Systematic radiomanometry in our last series of 700 cholecystectomies involving patients who presented no lithiasis in the common duct enabled us to diagnose odditis in 8 per cent of cases. The presence of odditis was verified histologically.

Manometry plays a vital part in this diagnosis and in every case enables the postcholecystectomy syndrome to be avoided, thanks to direct action on the choledochoduodenal junction. In fact, over a period of several years, only 4 postcholecystectomy syndromes have been noted among former patients who had not been subjected to peroperative radiomanometry as they had been operated upon at a time when this examination was not being carried out systematically.

On the other hand, we have had to reoperate upon 8 postcholecystectomy syndromes for which we were not responsible, in patients who had not had recourse to radiomanometry or for whom it had not been carried out properly, all of these presenting an odditis which explained all their troubles.

What surgical procedure should be utilized in the case of a high flow pressure through the sphincter of Oddi in spite of the amyl nitrite spasmolytic test? External drainage with a T tube in order to ease the sphincter is illogical, for it is impossible to discriminate between edematous odditis which may be reversible and sclerotic odditis, since the roentgenologic signs are generally not pathognomonic. Furthermore, in spite of cholecystectomy, it is not certain that a moderately impaired sphincter will not evolve progressively toward a retractile

sclerosis. Indeed, many postcholecystectomy syndromes appear several months after operation and become steadily worse.

Transpapillary drainage after dilatation of the sphincter is a procedure which was rejected after trial, for the following reasons: (1) The drainage needs to be continued for a long time—at least 2 to 3 months—with all the inconveniences this involves for the patient. (2) It is liable to lead to incidents or accidents, as was noted in a number of cases. (3) It does not absolutely preclude the possibility of a secondary retractile stenosis.

It therefore seems essential to act directly upon the sphincter, not blindly through the endocholedochal route—a procedure that has now been abandoned by its chief protagonist, Doubilet—but via the duodenal route. The reasons for our preference for total sphincteroplasty and not simple sphincterotomy which leaves the sphincter itself intact have already been stated.

*The sphincter of Oddi in lithiasis of the common bile duct.* A histologic examination of fragments resected from the sphincter has shown us that, in the majority of cases of common duct lithiasis, lesions ranging from edema to sclerosis are present in the sphincter muscle, these sometimes being only slight but sometimes involving a sclerous constriction of the opening. This finding has constituted an anatomopathologic argument for a return, in many cases of common duct lithiasis, to the practice of sphincteroplasty which offers the following considerable advantages:

1. Choledochotomy and external drainage are avoided; the extraction of calculi via the duodenal route after sphincteroplasty is easier and more complete than with a debilitating choledochotomy, whatever the number and size of the stones. When stones are present and it is not certain, in spite of a second cholangiographic check, that they have all been extracted, this large choledochoduodenal opening permits the elimination of any that may have been overlooked.

2. After 3 years, we have still not found any disadvantages in this method. Healing

FIG. 6. Lithiasis of the common bile duct. The flow pressure varies between 10 and 12 centimeters. Healing is quick and takes same time by ideal choledochotomy.

is quick and takes the same length of time as a simple cholecystectomy, even in the case of old or infirm patients, and no postoperative incidents occur which are directly ascribable to the operation. The long term results are good; there is no cholangiolitis due to reflux or no subsequent hepatic, pancreatic, or duodenal repercussions.

Our treatment of common duct lithiasis is not, however, restricted to total sphincteroplasty. We resort to three procedures all of which avoid external drainage, i.e., ideal choledochotomy, choledochoduodenostomy, and sphincteroplasty.

*The sphincter of Oddi in chronic pancreatitis.* Doubilet has long insisted on the role of the common channel of the pancreatic and bile ducts and the fact that, as a result of spasm, it is liable to give rise to chronic pancreatitis provoked by a reflux in Wirsung's duct.

We are of the opinion that organic odditis may be an important factor in the genesis

of such cases of pancreatitis. On many occasions, among patients presenting a picture of recurrent chronic pancreatitis or edematous pancreatitis, many lesions have been discovered affecting the whole of the gland. Not included among these are inflammations of the head of the pancreas which are very often associated with gallbladder lithiasis and regress after cholecystectomy. These lesions range from edematous pancreatitis to calcified or noncalcified sclerotic pancreatitis, pseudocysts, or partial necrotic pancreatitis.

Two types of lesions of the sphincter of Oddi have been revealed: (1) Stenosis of a long section of the common channel in the region of the sphincter of Oddi below a nonprotected and wide opening of Wirsung's duct which appears to be gaping when the sphincteroplasty is performed; this indicates pancreatitis provoked by reflux and hyperpressures occurring during sudden flashes of biliary hypertension. (2) True stenosis of the pancreatic opening over a length of 5 to 15 millimeters, more often than not associated with a stenosis of the sphincter of Oddi, but sometimes isolated; this indicates pancreatitis due to stasis resulting from some obstacle hindering the free flow of the external secretion.

In the first instance, sphincteroplasty is sufficient by itself; in the second, a sphincterotomy of the pancreatic duct must be added to the standard sphincteroplasty. This very effective procedure secures the relief of all pains of biliary and pancreatic origin.

## RESULTS

After 100 total sphincteroplasties performed over a period of 3 years, we were convinced beyond all question that this procedure involves no higher mortality rate than any other operation, even in serious cases. Of the 4 deaths recorded, only 1 could be ascribed to the method.

Subsequently, many other investigators have stressed the striking and apparently paradoxic simplicity of the results. This 2 to 3 hour operation usually has after-effects that are less complicated than those of a simple cholecystectomy. The only fear was whether the lasting mutilation of the choledochoduodenal junction would lead to the appearance of hepatopancreatic organofunctional disorders. As months and now years have passed, this apprehension is proving groundless.

All of our patients have been followed up clinically. In every case except 1 in which a mistake was made in the operative approach, the results have been classified as either excellent or good, depending on whether or not a diet is necessary.

No cholangiolitis has been noted in spite of the fact that any reflux can always be revealed by the ingestion of barium. We were not able to follow up all of our patients for a long period after operation as they did not see the need for such clinical examinations. Many of them, however, were given roentgenologic check-ups—intravenous cholangiography, ingestion of barium—and a few had biologic or even histologic tests, i.e., liver biopsy. The results of these examinations all showed the long term benignity of total sphincteroplasty; there are no repercussions on the liver provoked by reflux or by a modification of the intrabiliary pressures, hypertonia in particular.

As for the pancreatic consequences of the excision of the sphincter, these need not cause too much concern. The section of the sphincter eliminates all possibility of biliary hypertension—a condition which is often noxious in dystonias of the sphincter—without involving any pancreatic reflux or hypertonic disorders, for the persistence of a functional Wirsung sphincter is always noted in the opening of Wirsung's duct, which we always located during the sphincteroplasty.

## CONCLUSION

By overthrowing traditional concepts and long-standing surgical habits, the operative suppression of a sphincter action at the anastomosis of the biliopancreatic duct has given rise to much controversy.

The very principle of such a mutilation is

liable to shock at first sight but surgery has a mutilating rationale and far more anti-physiologic procedures, gastrectomy, for example, have been accepted in the light of the results they give. Moreover, the sphincter is not found consistently in all animals but seems to be connected only with the cholecyst; the horse has no gallbladder and it has no sphincter of Oddi.

The practice of this resection of the sphincter, both as regards its preoperative choice and its actual performance, can only be recommended to experienced surgeons who have ample radiologic, anesthetic, and postoperative facilities at their disposal, and it would be dangerous to bring it into wide use too rapidly.

But, after a period of 3 years, we may conclude that this experimental procedure gives results that are very worth while from the therapeutic point of view and that it opens up wide nosologic perspectives.

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# SIGNIFICANT POSTMENOPAUSAL ENDOMETRIOSIS

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ENDOMETRIOSIS seldom is diagnosed clinically in postmenopausal women because it is generally believed that the endometriotic process in older patients undergoes atrophy and its clinical features gradually fade away with the advent of the menopause. However, casual review of the records in the files of the Mayo Clinic disclosed that a number of patients had symptomatic postmenopausal endometriosis. Therefore, this study was undertaken to investigate, from the clinical and histologic aspects, both internal and external endometriosis in postmenopausal women, with particular attention being given to those instances in which the growth was considered significant.

## GENERAL BACKGROUND

Scott and Te Linde reported upon 13 patients with postmenopausal endometriosis in a series of 516 patients of all ages who had the external form of this disease. Only 1 postmenopausal patient was operated upon primarily for endometriosis. They thought it was surprising that more postmenopausal endometrial cysts were not encountered.

Colcock and Lamphier, reporting on endometriosis treated surgically, found 7 patients beyond the menopause who were seen because of significant symptoms. Complaints in these instances were related to distortion of the pelvic viscera as a result of the endometriotic process and were no longer of the cyclic character which is so typical of endometriosis in younger women.

Henriksen found 37 examples of postmenopausal endometriosis in a review of 1,000 cases of endometriosis. Interestingly, 29 of these 37 patients had undergone previous complete bilateral oophorectomy, yet active endometrial tissue was found in all 29. Six of the 37 patients underwent radical operations for suspected neoplasm of the large intestine. The clinical possibility of endometriosis was not considered in any of these 37 patients. Other authors have reported examples of postmenopausal endometriosis causing intestinal obstruction that roentgenologically often resembled malignant disease. When the process involved the terminal part of the ileum, the symptoms sometimes suggested intermittent obstruction or even acute appendicitis.

One of the most intriguing aspects of endometriosis concerns its possible transformation into a malignant lesion. Carcinoma, so engendered, may not be discovered until long after the menopause.

Frank and Geist, and Emge reported studies on postmenopausal uterine adenomyosis and indicated that the lesions were not of clinical importance in this age group. However, Bennet, who combined internal and external postmenopausal endometriosis, found a high incidence of postmenopausal bleeding in these patients. In rare instances, as reported by Kumar and Anderson, adenomyosis undergoes malignant transformation, and these carcinomas can occur after menopause.

The explanation for "activity" in postmenopausal endometriosis is thought to lie in persistence of a significant level of estrogen after menopause, although the exact

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source of the estrogen is speculative. Paulsen and his associates indicated that in postmenopausal women twice as much estrogen was excreted than occurred in ovariectomized patients. Studies by Struthers, and Greenwood and Bulbrook on the adrenal gland as a source of estrogen in postmenopausal women have shown that in some instances excretion of small amounts of estrogen continues even after bilateral oophorectomy and adrenalectomy. The persistence of estrogen after adrenalectomy may be due to the presence of aberrant adrenal cortical tissue. Struthers pointed out that another origin may be the pituitary gland, a known source of estrogen in cattle and horses.

## MATERIALS AND METHODS

A review was made of the records of all women seen at this clinic from 1945 through 1958 who were 45 years of age or older and who were at least 2 years postmenopausal at the time that a diagnosis of external endometriosis was established either grossly or microscopically. Those patients in whom amenorrhea had been produced by hysterectomy without bilateral oophorectomy have been excluded.

From this group of 136 women, 39 were selected who had postmenopausal endometriosis that was deemed to be clinically significant; 2 patients encountered during 1959 with similar conditions were added to the study later. The criteria of "clinical significance" hinged on the presence of substantial intestinal endometriosis, widespread pelvic endometriosis, making operation more difficult, or ovarian endometrial or tarry cysts more than 3 centimeters in diameter which had been removed because of either symptoms or the suspicion of malignancy. A group of 22 patients with postmenopausal internal endometriosis—adenomyosis—were added later without regard to clinical importance because many of these lesions were of histologic interest in this investigation.

The surgical specimens, preserved in 10 per cent formalin, were examined, with special attention to the size, color, consistency, location and, when feasible, the weight of the external endometriotic lesions, endometriomas, or uteri with adenomyosis. When the ovaries were included, these organs were examined carefully for the presence of follicular cysts, in contrast to simple complete atrophy.

Blocks of tissue were removed from selected parts of each specimen of external endometriosis, chocolate cyst, and adenomyosis. This tissue was embedded in paraffin, and sections were prepared and stained with hematoxylin and eosin.

Sections were made of the endometrium in those 16 cases of endometriosis in which the uterus was available for study to allow histologic comparison of this tissue and that affected by endometriosis. In the aforementioned 22 uteri with adenomyosis, blocks of tissue were cut, with preservation of endometrium on one border, which served not only for the study of the endometrium but also as an indication of the depth to which adenomyosis had penetrated.

The study included only those patients in whom microscopic proof of endometriosis was present, defined as endometrium-like glands surrounded by stroma, and those patients with adenomyosis in whom glands and stroma were more than 1 low power (×50) microscopic field below the endometrium. Retained also for purposes of comment were patients who had significant chocolate cysts for which proof of endometriotic origin could not be established microscopically.

To study the incidence of external endometriosis, we examined 50 uteri obtained at consecutive necropsies from patients who had been menopausal for at least 2 years. Sections for microscopic study were made from 3 or more blocks of tissue removed from the posterior serosal surfaces of these uteri, often from white scarred zones which were almost unsuspected of being endometriosis.

TABLE I.—NATURE OR SITE OF SIGNIFICANT POSTMENOPAUSAL EXTERNAL ENDOMETRIOSIS IN 26* CASES PROVED HISTOLOGICALLY AND 15 UNPROVED

| | *Clinical category of endometriosis* | | |
|---|---|---|---|
| | | *Asymptomatic* | |
| *Nature or site* | *Symptomatic* | *Primary cause for operation* | *Found at operation for other causes* |
| Ovarian endometriomas | 1 | 4 | 5 |
| Unproved tarry ovarian cysts. | 5 | 4 | 6 |
| Diffuse | 1 | — | 6 |
| Intestine | 2 | — | 6 |
| Vagina | — | 1 | — |
| Total | 9 | 9 | 23 |

*Includes 2 patients seen in 1959.

TABLE II.—AGES AT OPERATION OF PATIENTS WITH SIGNIFICANT POSTMENOPAUSAL ENDOMETRIOSIS—41 EXTERNAL AND 22 INTERNAL

| | *Ovarian endometriomas* | | | | | |
|---|---|---|---|---|---|---|
| *Age, yrs.* | *Proved* | *Unproved* | *Diffuse* | *Intestine* | *Vagina* | *Adenomyosis* |
| 75–79 | 1 | — | — | — | — | — |
| 70–74 | 1 | — | 1 | — | — | 1 |
| 65–69 | — | 1 | 1 | — | — | 3 |
| 60–64 | 1 | 5 | — | 1 | — | 1 |
| 55–59 | 5 | 5 | — | 2 | 1 | 14 |
| 50–54 | 1 | 2 | 4 | 4 | — | 2 |
| 45–49 | 1 | 2 | 1 | 1 | — | 1 |
| Total | 10 | 15 | 7 | 8 | 1 | 22 |

## CLINICAL FEATURES

*Incidence.* Of the 136 instances of external endometriosis, 39 (29 per cent) were of clinical significance, whereas in the remainder the findings were incidental. A total of 24 of the 39 clinical lesions (18 per cent) were proved histologically to be endometriosis, while the other 15 lesions were chocolate cysts the origin of which was strongly suspected of being endometriosis but in which diagnosis could not be verified microscopically. Four (3 per cent) of the 136 patients with postmenopausal endometriosis were symptomatic; this category is increased to 9 patients (7 per cent) when symptomatic chocolate cysts are included. When the 9 patients (7 per cent) with sizeable asymptomatic endometriotic lesions requiring exploration are added to this group it makes a total of 18 patients, or 14 per cent of the entire series of 136.

The lesions in 2 of the 22 examples of adenomyosis were of clinical significance, whereas in the remainder the findings were incidental.

In the group of 50 uteri obtained at necropsy, 7 (14 per cent) had foci of atrophic endometriosis.

*Site.* Table I summarizes the nature or site of the endometriotic lesions and their clinical categories. A total of 26, rather than 24, histologically proved lesions is indicated because 2 specimens are included which were studied in 1959.

*Age.* The oldest patient with significant external endometriosis was 79 years, and the oldest with adenomyosis was 73. The age incidence is summarized in Table II.

*Past history.* Note was made of any symptoms which occurred during the reproductive years that could have been attributable to endometriosis. Seldom were such complaints elicited, probably because of the fact that menstrual discomforts were forgotten after their complete cessation. When patients with proved external endometriosis did mention previous discomfort, dysmenorrhea was the symptom most commonly recalled, with menorrhagia, backache, and severe molimina being less frequent. The incidence of absolute sterility in the patients who had external endometriosis was 39 per cent, whereas in those with adenomyosis it was 5 per cent.

Approximately one-half of the patients with proved external endometriosis had undergone previous pelvic operations. Six of the 8 patients with endometriosis involving the intestine had been subjected to previous pelvic operations; however, in only 2 of these 6 patients was the endometriosis symptomatic.

One patient with external endometriosis and 3 with adenomyosis recently had received exogenous estrogenic hormones.

*Signs and symptoms.* The first clinical category, or group, comprised the 9 patients who had symptomatic endometriosis, proved or unproved histologically (Table I). A diagnosis of endometriosis was entertained preoperatively in only 2 patients. The patients who had large cysts complained pri-

marily of pelvic pain that usually was confined to one quadrant of the lower part of the abdomen. This pain was often intermittent or crampy and had been present for periods varying up to a year. The symptoms in 1 patient suggested torsion of a cyst, while in another, in whom the cyst recently had ruptured, the inflammatory reaction suggested diverticulitis or carcinoma of the rectum. In 2 instances, endometriosis had produced almost complete obstruction of the small intestine when complaints were those of intermittent abdominal pain and distention.

The second group, also 9 patients, was made up of those who had sizeable asymptomatic lesions requiring exploration (Table I). In each instance, the physician urged operation, since the possibility of malignancy could not be excluded in the face of relatively large ovarian lesions.

The third group, 23 patients (Table I), comprised those in whom endometriotic lesions of significance were encountered during operations for other conditions, such as malignant tumors of the uterus or colon, with the symptoms and indications for surgical intervention being caused by these other lesions.

As already noted, 2 patients with adenomyosis had significant symptoms. One, who was 5 years past the menopause, complained of episodic pain in the left lower part of the abdomen of 1 year's duration; during these attacks, she had noted a reddish brown vaginal discharge. Examination disclosed a small mass behind the uterus. Multiple adenomyomas were the only operative finding. The other patient, menopausal for 4 years, had experienced an unusual course of events. After uterine curettage followed by laparotomy for postmenopausal bleeding, a diagnosis of widespread pelvic cancer was made. Re-exploration, however, disclosed a subinvoluted uterus containing diffuse adenomyosis. The endometrium was atrophic.

*Treatment.* The usual surgical treatment for endometriomas was bilateral salpingo-oophorectomy and hysterectomy. The contralateral ovary was preserved in a few selected instances. Although all patients with "diffuse" pelvic endometriosis underwent hysterectomy and bilateral oophorectomy, the endometriosis was incidental in all but 1 instance.

FIG. 1. Endometriosis of ileum in a 50 year old female, postmenopausal for 4 years. Although atrophic histologically, this lesion produced obstruction of the small intestine. Hematoxylin and eosin, ×72.

Of the 8 patients who had intestinal endometriosis, 2 had obstruction of the small intestine, which was treated by removal of all remaining ovarian tissue and separation of intestinal adhesions. Resection of the intestine was not deemed necessary. In the 6 others, who had colonic endometriosis, the primary disease with which the endometriosis was associated often necessitated resection of a segment of colon.

The 2 patients with adenomyosis in whom this lesion was the primary cause of the signs and symptoms underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy.

## PATHOLOGIC FEATURES

*Gross appearance.* Endometriomas in these postmenopausal patients appeared grossly, much as did those in younger patients. The diameters of the 10 endometriomas ranged from 3 to 10 centimeters; the cysts were ovoid and unilocular, frequently being filled with a considerable amount of chocolate colored material. Rarely were these ovarian

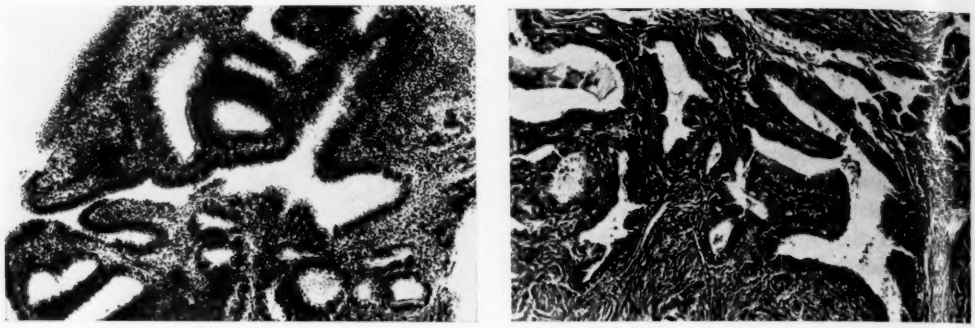

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FIG. 2. a, Large (9 by 8 by 7 cm.) significant, although asymptomatic, endometrioma in a 59 year old female postmenopausal for 6 years. Note the moderate cellular activity of both glands and stroma, although the patient was not receiving exogenous estrogen. Hematoxylin and eosin, ×65. b, Endometriosis in a 52 year old female, postmenopausal for 7 years. The lesions were scattered over the posterior aspect of the uterus and the adnexa which made hysterectomy for adenocarcinoma of the uterus more difficult. Note the moderate activity of glands and stroma, even though the patient was not receiving exogenous estrogen. Hematoxylin and eosin, ×77.

endometriomas free from surrounding adhesions, the attachments often being to the uterus and other pelvic viscera.

In those lesions designated in this study as "diffuse," the gross appearance was one of thick adhesions which involved the adnexa and the posterior uterine serosal surface. Their endometriotic nature was indicated by puckered, bluish black foci ranging in size from a pinpoint to 4 or 5 millimeters in diameter, diffusely scattered over the pelvic tissues.

The gross appearance of the intestine involved by endometriosis was striking. One patient, with long-standing intermittent intestinal obstruction, had endometriotic fixation of the terminal 120 centimeters—4 feet—of ileum to the abdominal wall, as well as to itself and to the uterus. A second patient, with recent onset of symptoms, had endometriosis of long standing involving the ileum at a point 10 centimeters from the ileocecal valve, with almost complete mechanical obstruction. In the other instances of intestinal endometriosis, generally the lesions were found on the colon as thick indurated nodules approximately 2 centimeters in diameter, with consequent kinking of the intestinal wall.

In the 1 patient with endometriosis, the vagina had a velvety firm plaque on the posterior upper vaginal wall that was suspected of being a malignant lesion.

The gross appearance of postmenopausal adenomyosis did not differ from that in other age groups. The average weight of the uteri affected by adenomyosis, which were free of myomas and had been removed from patients who were not receiving exogenous estrogens, was 115 grams. Since normal uteri weigh approximately 100 grams, this indicates that subinvolution frequently accompanies adenomyosis, even after menopause.

*Associated pathologic lesions.* Although various pelvic malignant tumors were associated with external endometriosis in 14 patients, all but 1 of the operations in these 14 instances were performed for known or suspected pelvic carcinoma, and thus this association is of little significance. One patient had a 2 kilogram granulosa cell tumor of the ovary associated with endometrial adenocarcinoma and diffuse endometriosis on the posterior serosal surface of the uterus.

Likewise, 4 patients with adenomyosis had associated pelvic malignant tumors that constituted the primary indication for oper-

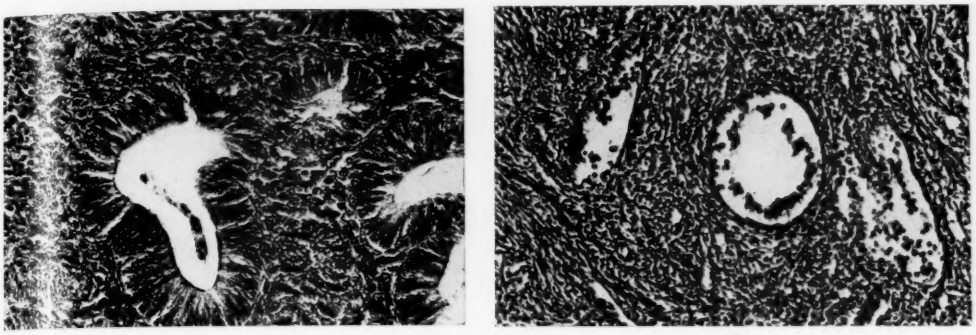

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FIG. 3. a, Adenomyosis in a 55 year old female, postmenopausal for 6 years, who was not receiving exogenous estrogen. Note the moderate glandular and stromal activity. Hematoxylin and eosin, ×205. b, Adenomyosis in a 73 year old female, postmenopausal for 28 years. Note the pronounced atrophy of glands and stroma. Hematoxylin and eosin, ×155.

ation. One of these malignant tumors was a granulosa cell carcinoma of the ovary.

We noted a 50 per cent incidence of myomas associated with external endometriosis and a 32 per cent association of myomas with adenomyosis.

*Microscopic findings.* The glands and stroma in each specimen were graded according to "activity" as being atrophic, slightly active, or moderately active. Atrophic glandular epithelium varied from flattened columnar to columnar types, with clear cells present as evidence of the müllerian origin. Cilia were noted in some instances. The nuclei were small, with an absence of mitotic figures. The atrophic stroma generally was sparse, the cells being of the spindle type, with varying degrees of fibrosis. Stellate cells and mitotic figures were absent. Slightly or moderately active glandular epithelium exhibited a corresponding increase in activity as evidenced by taller columnar epithelial cells with more abundant cytoplasm and cilia, and particularly by larger nuclei and nucleoli, with occasional mitotic figures. Similarly, the stromal elements in tissue of these grades of activity were more abundant. Stellate cells predominated over spindle cells and were larger, with increasing nuclear size and mitotic activity. As is to be expected, progestational epithelium was not encountered in this study.

In 21 of the 26 histologically proved lesions, the endometriosis was classed as atrophic; this included all 8 instances of intestinal endometriosis (Fig. 1). The remaining 5 lesions exhibited activity of varying degrees (Fig. 2); in none of the 5 patients concerned was the endometriosis symptomatic. One of these 5 patients recently received exogenous estrogen.

Ten of the series of 22 adenomyomatous uteri presented histologic evidence of activity of the ectopic endometrium (Fig. 3a), whereas the endometrium in the others was atrophic (Fig. 3b). Two of the 10 patients so affected received exogenous estrogen.

One example of low grade ovarian cystadenocarcinoma occurring in close association with endometriosis suggested strongly its origin in endometriosis, although all the criteria for proof of the development of a malignant tumor from ovarian endometriosis, as outlined by Sampson and by Scott, could not be satisfied from examination of the tissues (Fig. 4a). Still another ovarian neoplasm surrounded by ancient endometriosis was found to be a cystadenofibroma (Fig. 4b), an association which has been noted often. This may represent the origin of cystadenofibroma in endometriosis.

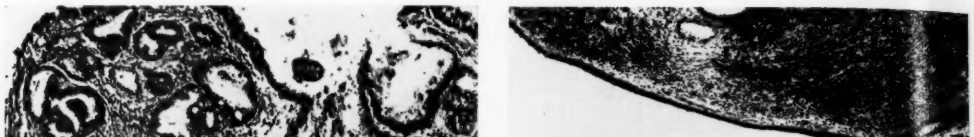

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FIG. 4. a, Endometriosis, bottom center, in a 56 year old female, postmenopausal for 2 years. At upper left, associated grade 1 cystadenocarcinoma, which probably originated in the endometrioma. Hematoxylin and eosin, ×65. b, Atrophic postmenopausal endometriosis in a 79 year old female. The endometriosis surrounded a benign papillary cystadenofibroma, and possibly gave origin to the latter lesion. Hematoxylin and eosin, ×43.

COMMENT

Scott and Te Linde found that 47 per cent of 516 surgical patients with endometriosis in all age groups were operated on primarily for endometriosis. When this is compared with the incidence of approximately 14 per cent in our patients, it appears that postmenopausal patients are operated on primarily for endometriosis approximately one-fourth to one-third as frequently as are younger patients with endometriosis.

The importance of individualizing the treatment of patients with endometriosis, even in this older age group, should be emphasized. Castration is a satisfactory and correct treatment, and conservative management of involved intestine is usually possible. Counseller noted the difficulties in the surgical treatment of patients with diffuse and extensive pelvic endometriosis, cautioning that complications such as vesicovaginal fistulas, ureteral injuries, intestinal fistulas, and obstruction may occur unless meticulous care is used.

Those patients in our study in whom activity of the ectopic endometrial glands continued postmenopausally probably had a significant persistence of circulating estrogen. Tending to confirm this theory is the fact that the uterine endometrium showed evidence of cellular activity, in the form of either cystic glandular hyperplasia or a cystic proliferative endometrium, in all but 2 patients who had a significant degree of activity in the zones of adenomyosis or endometriosis. The lesions in these 2 exceptions were associated with endometrial carcinoma, an association that may be of hormonal significance. The histologic aspects of the 16 cases of endometriosis in which the uterus was available for study (none of these patients having received exogenous estrogens) were classified as follows: atrophic, with atrophic endometrium in 6 cases, with proliferative cystic endometrium in 2 cases and with endometrial carcinoma in 4 cases; slightly active, with atrophic—very slightly active—endometrium in 1 case; moderately active, with proliferative cystic endometrium in 1 case and with endometrial carcinoma in 2 cases. The histologic aspects of the 22 cases of adenomyosis were classified as follows: atrophic, with atrophic endometrium in 10 cases, with cystic glandular hyperplasia of endometrium in 2 cases—in 1 of these exogenous estrogen was given; atrophic and slightly active, with atrophic endometrium in 2 cases; slightly active, with proliferative cystic endometrium in 2 cases; moderately active, with cystic glandular hyperplasia of endometrium in 2 cases and with proliferative

cystic endometrium in 4 cases—in 2 of these instances exogenous estrogen was given.

A major source of the estrogen in 1 patient with external endometriosis and 3 patients with adenomyosis was known to be exogenous. In 1 patient with adenomyosis, the source was probably an ovary containing follicular cysts. In other patients, although the ovary may have been the source, an extraovarian depot remained a distinct possibility. Two patients with granulosa cell tumors and 1 patient with ovaries typical of the Stein-Leventhal syndrome, which had produced proliferative endometrium, failed to show activity in the ectopic endometrium. Three other patients, 1 receiving exogenous estrogen, in addition to the 1 with the Stein-Leventhal syndrome, exhibited cellular activity of the endometrium and yet failed to show cellular activity in the ectopic endometrium. The fact that there are occasional patients with differences in the end-organ response does not negate the fact that a definite hormonal relationship probably exists.

Examples of the numerous possible fates of endometriosis were encountered in this study. In many patients, the zones of endometriosis had become white and had almost vanished, leaving only a slightly puckered area in which atrophic endometriosis could be found microscopically. In others, the walls of the endometriomas had become so thinned and the epithelium so flattened that it was histologically difficult or impossible to prove the lesions to be endometriosis. Other cysts had ruptured and collapsed. As already noted, endometriosis may have produced a cystadenofibroma in 1 instance and cystadenocarcinoma in another. In many patients, foci of endometriosis did not achieve any clinical significance, whereas, in a sizeable group, endometriosis was anything but symptomatically silent.

## SUMMARY AND CONCLUSIONS

A study was made at the Mayo Clinic of 136 cases of external endometriosis, established grossly or microscopically, in postmenopausal women. Endometriosis can be clinically important after the menopause. Clinically significant endometriosis, proved microscopically, was present in 24 (18 per cent) of these 136 cases. This incidence reached 29 per cent when chocolate cysts, whose suspected cause could not be verified as endometriosis, were included.

The commonest site of significant postmenopausal endometriosis was the ovary. Three-fourths of all lesions considered clinically significant involved the ovary or intestine. The high incidence of patients with intestinal endometriosis who previously had undergone pelvic operations might indicate that this is a possible hazardous sequel to such operations in patients with endometriosis.

The diagnosis of endometriosis was made preoperatively in only 2 of the patients who had significant external endometriosis.

Castration was the principal form of definitive surgical management, with conservative management of involved intestine when possible. Patients who have postmenopausal endometriosis are operated upon primarily for endometriosis one-fourth to one-third as frequently as are younger women with endometriosis.

Approximately one-fifth of all patients with clinically significant and histologically proved postmenopausal endometriosis exhibited histologic evidence of cellular activity in the ectopic foci. In none of these patients was the endometriosis symptomatic. Many foci of insignificant ectopic endometrium also continue to show some histologic activity after the menopause. Endometriosis was found on the posterior uterine serosal surface in 7 of 50 consecutive necropsies on postmenopausal women. Inactive and clinically insignificant endometriosis often is not identified grossly as such.

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# SEXUAL FUNCTION AND FECAL CONTINENCE FOLLOWING ABDOMINOPERINEAL RESECTION OF RECTOSIGMOID FOR ACQUIRED MEGACOLON

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THE USE of abdominoperineal rectosigmoidectomy in the treatment of various rectocolic diseases has presented, among others, the problem of possible alterations in sexual function as well as that of fecal incontinence after such operations. These complications have been referred to in the literature.

In the surgical treatment of cancer of the rectum, these problems assume an importance which is up to a point secondary because, according to the site of the lesion, adequate resection is not always compatible with preservation of the sphincter. On the other hand, removal of the lymphatic system of this region will certainly result in extensive damage to the small nerve fibers leading to the genital organs.

However, as regards benign affections, such as congenital or acquired megacolon, extirpation of the rectosigmoid is effected without interfering with the sphincters, and a careful dissection made close to the rectum can avoid damaging the small nerve fibers responsible for sexual function.

Several investigators have dealt with these problems. Cutait refers to sexual impotency in 3 patients who were submitted to abdominoperineal rectosigmoidectomy for megacolon; whereas, of 20 other patients in whom the abdominal method alone was used, only 1 complained of loss of ejaculation. He also records that in 47 patients submitted to operation by the exclusively abdominal method not 1 presented fecal incontinence, whereas this complication occurred in 12 instances in which abdominoperineal resection was used. In 9 of these patients, incontinence was only temporary and disappeared within a few weeks; however in the other 3 patients the period varied from 7 to 8½ months. Such results would be ascribed to a more extensive dissection with more ample resection of the rectum when the abdominoperineal method is employed.

Hallenbeck and Waugh believe that resection of the rectum in adult males is followed by a high incidence of impotence, although exact figures regarding its frequency have not been obtained.

Petit and Decaudevaine analyzed the results of 18 cases of congenital megacolon in which the Swenson operation was used. Of this series 3 patients showed anal incontinence.

Gaston (2–4) made a series of experiments and clinical observations on the mechanism of fecal continence. He admits the existence of a rectocorticoanal reflex which, by means of stimuli originating in the rectal wall and reaching the cortex, causes consciousness of a desire to evacuate. The cerebral cortex sends out the efferent stimuli which reach the external anal sphincter, which is the principal agent responsible for the mechanism of anal continence, through the inferior hemorrhoidal nerves, thereby setting up their contraction or relaxation. It is admitted that the internal sphincter of the anus has no definite function in the mechanism of fecal continence. Rectal stimulation would occasion relaxation of this muscle and perhaps an active dilation of the canal,

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thus preparing it for the passage of fecal material. In the absence of rectal stimulation the internal anal sphincter perhaps contributes toward the tonic closing of the anus. According to Gaston, sphincteral integrity alone is not sufficient for the maintenance of fecal control, but it is also necessary to retain a segment of rectum varying from 1 to 7 centimeters—the precise length not yet having been determined—in which the anastomosis may be made without interfering with the afferent course of the reflex mentioned. He believes, therefore, that the rectum is an integral part of the sphincteral mechanism.

Goligher made a study of 179 patients operated on for carcinoma, rectal prolapse, and ulcerative colitis and concluded that in order to maintain fecal control the anastomosis should be made at least 6 centimeters above the anal orifice.

Swenson analyzed a 10 year follow-up study of 200 patients suffering from congenital megacolon who had been operated on by his technique and verified that of 14 male patients of sexual maturity 8 subsequently married and fathered children and the remaining 6, still bachelors, did not show any loss of power to ejaculate. On the other hand, lack of fecal control did occur in some cases; this, however, rarely persisted for more than 2 or 3 weeks. Swenson admits that these problems do not constitute any obstacle to making the resection with anastomosis even 2 centimeters above the pectineal line.

## MATERIAL AND METHOD

This article is based on a clinical study of the sexual activities and fecal control of 40 patients who suffered from acquired megacolon and were submitted to abdominoperineal rectosigmoidectomy. Clinical observations and recent epidemiologic and experimental findings in this country strengthen the hypothesis that the etiologic agent of acquired megaesophagus and megacolon observed in Brazil is the same as that which causes Chagas' disease, the Trypanosoma cruzi. These inquiries were always made during a period which varied from 1 month to 10 years after the operation. Of these patients 30 are males and 10 females, all of whom have attained sexual maturity.

## SEXUAL ACTIVITY

An inquiry was made into the sexual behavior of these patients before the appearance of the symptoms of the disease, during its evolution, and after the abdominoperineal rectosigmoidectomy.

In the 30 male patients, libido, erection, orgasm, and ejaculation were normal before the onset of the malady. During the evolution of the disease and after the performance of the operation the sexual behavior of these patients was as follows:

1. Twelve patients, 40 per cent, remained sexually normal both throughout the development of the disease and after the operation.

2. Eleven patients, 36.66 per cent, showed diminution of sexual potency during the development of the disease. This, however, was of a temporary character and potency became completely normal again after the operation.

3. Three patients, 10 per cent, showed a decrease of seminal discharge during the evolution of the malady. In 1 of the patients there was a progressive decrease of seminal fluid until its complete disappearance 8 years before the operation when the patient had attained the age of 46 years. After the abdominoperineal rectosigmoidectomy the decrease of seminal discharge still continued in these patients, although their erection, libido, and orgasm remained normal.

4. Three patients, 10 per cent, showed a marked decrease of erection, libido, and orgasm before the rectosigmoidectomy and after the operation became sexually impotent. The follow-up in these cases was for periods of 4 months, 5 months, and 4 years and 10 months, respectively.

5. Only 1 patient, 3.44 per cent, who had normal sexual function during the evolution of the disease, showed decrease of sexual potency and loss of power of ejaculation.

This was a man 36 years of age whose case was followed up for 12 months.

In the 10 female patients the analysis was of their sexual behavior with respect to libido and orgasm before the disease, during its evolution, and after abdominoperineal rectosigmoidectomy. The results were as follows:

1. Two patients, 20 per cent, remained sexually normal both during the disease and after the operation.

2. One patient, 10 per cent, who was a spinster before and during the disease married after the operation and is sexually normal.

3. Two patients, 20 per cent, who were normal before contracting the disease, became sexually frigid during its course; after the operation, however, their normal sexual activities were resumed.

4. Three patients, 30 per cent, were sexually frigid before contracting the disease and remained so both during its evolution and after the operation.

5. Only 2 patients, 20 per cent, who were sexually normal before the malady, became sexually frigid during its development, and continued so after the operation.

Furthermore, 2 of the 10 patients became pregnant after the rectosigmoidectomy. Both the pregnancies and the births were normal.

### FECAL CONTINENCE

As regards fecal continence after rectosigmoidectomy we obtained the following results:

In 32 patients, 80 per cent, fecal continence remained normal even in the immediate postoperative period. In 8 cases, 20 per cent, temporary fecal incontinence for liquid stools occurred during periods varying from 3 days to 4 months. There was no case in which fecal incontinence for solid feces manifested itself.

The height of the rectosigmoidal anastomosis was made at different levels from the mucocutaneous line as follows: 3 centimeters in 5 cases; 4 centimeters in 4; 5 centimeters in 16; 6 centimeters in 9; 7 centimeters in 3; and 8 centimeters in 3.

In the 8 patients who had temporary fecal incontinence, the rectosigmoidal anastomosis was made at different levels from the mucocutaneous line. No intimate relation was established between the duration of incontinence and the smaller segment of rectum left intact.

In the first patient the height of the anastomosis was at 3 centimeters and incontinence lasted 15 days; in the second at 4 centimeters with temporary incontinence; in the third at 5 centimeters with 3 days of incontinence; in the fourth at 5 centimeters with 20 days; in the fifth at 6 centimeters with 30 days; in the sixth at 6 centimeters with 30 days; in the seventh at 6 centimeters with 120 days; in the eighth at 7 centimeters with 7 days of incontinence.

We also endeavored to verify if there was any relation between fecal incontinence and some preoperative traumatism due to possible attempts to remove a fecaloma via the anus by digital manipulation, an operation frequently resorted to in patients suffering from megacolon when they present intestinal occlusion or subocclusion due to hardened fecal matter at rectal level. However, this happened in only 1 of the 8 cases.

### COMMENT

The study shows that 23 male patients presented no sexual alteration attributable to rectosigmoidectomy. In 3 patients in whom decrease of ejaculation occurred, having in 1 case disappeared entirely, such condition had existed before the operation and remained unchanged afterward. In 3 cases, 10 per cent, impotentia coeundi occurred after the operation. These patients, however, admitted to having observed a distinct decrease in sexual potency before the operation. In these cases, surgical intervention intensified a pre-existing deficiency. In only 1 case, 3.34 per cent, in which sexual activities were normal before the rectosigmoidectomy, did decrease in sexual power and loss of ejaculation occur.

With regard to the female patients, in 5 cases or 50 per cent no sexual disturbance whatever occurred after the operation. In 3 cases, 30 per cent, there had been sexual frigidity both before and during the evolution of the malady. This remained unaltered after the operation which cannot be blamed. Only 2 patients, 20 per cent, showed sexual frigidity after the operation although that condition had been marked before surgical intervention, that is, during the evolution of the disease.

To interpret these findings three hypotheses may be formulated:

1. Psychogenic factor which may or may not be caused by the disease and be responsible for the sexual depression referred to in the preoperative period, which subsequently disappears or which may persist in some cases after the operation given the emotional instability and autosuggestion of these patients. Such a factor would explain the normalization of sexual functions after operation, a normalization which occurred in 11 male patients, 36.66 per cent, and in 2 female patients, 20 per cent, all of whom had complained of distinct decrease in sexual activity before the operation.

2. Traumatic factor resulting from injury to the small nerve fibers leading to the genital organs as a consequence of surgical trauma. The greater the area of perirectal fat dissected, the greater this will be, for which reason such dissection should always be effected close to the rectal wall. This eventuality probably occurred in 3 patients who suffered from sexual depression before the operation, and most certainly occurred in 1 case in which the patient was sexually normal before the operation and subsequently complained of decrease in the power of erection with loss of ejaculation.

3. Destruction of nerve fibers due to the etiologic agency of the disease itself with probable damage to the sympathetic and parasympathetic nerve cells responsible for the mechanism of erection and ejaculation, a destruction identical to that which occurs in the myenteric plexus of the gastrointestinal tract in sufferers from acquired megacolon and megaesophagus. This hypothesis seems tenable as it alone can explain the decrease of ejaculation in 2 patients and even its absence in 1 of the patients, which manifested itself during the evolution of the disease and persisted without becoming worse after the abdominoperineal rectosigmoidectomy, although erection, libido, and orgasm remained normal. This decrease in ejaculation began at 34 years of age in 1 of these patients, the seminal discharge having disappeared completely 8 years before the operation, that is, at 46 years of age. The cause of this disturbance can be ascribed to a lesion of the sympathetic nerve fibers responsible for the mechanism of ejaculation, with diminution of the peristalsis of the deferent ducts and seminal vesicles. These lesions would have the same etiologic agent that causes acquired megacolon. It has a predilection for the autonomous nervous system. The destruction of the myenteric plexus of the gastrointestinal tract in the esophagus, stomach, duodenum, and colon, and of the urinary system in the ureters, is proof of this fact. Further studies should prove whether this same etiologic agent can cause damage to the intramural sympathetic fibers of the seminal vesicles and of the deferent ducts.

As regards fecal continence, the present study proved that in no case did abdominoperineal rectosigmoidectomy cause permanent fecal incontinence. Moreover, only 20 per cent of the patients analyzed had fecal incontinence for liquid stools which was of a temporary character of from 3 to 120 days.

Some investigators have advocated the necessity of leaving a rectal stump of at least 6 centimeters in order to preserve the rectocorticoanal reflex which is responsible for the conscious mechanism of evacuation. In our series, fecal incontinence, although of a transitory nature, continued for longer periods in the cases of those patients in whom the anastomosis was made at this level, whereas in various cases in which the anastomosis was effected at 3 or 4 centimeters no fecal incontinence occurred.

The interpretation of the sexual alterations shown during the evolution of acquired megacolon and after abdominoperineal rectosigmoidectomy is a complex matter needing further detailed study.

However, some points of practical interest deserve to be kept in mind for the technique used in rectosigmoidectomy. We believe that dissection of the rectum should be made by means of scissors and close to the muscular wall in order to avoid any extensive damage to the small sympathetic and parasympathetic nerve fibers which proceed from the hypogastric plexus in the direction of the genital organs. Manual liberation of the posterior rectal wall is not advised since such untimely action might result in much greater damage to the said nerve fibers than would result from a carefully made dissection by scissors.

An interesting fact to which we wish to draw attention and which was demonstrated in 3 of our patients is the possibility of damage to the sympathetic nervous system governing the genital region by the same etiologic agent which causes acquired megacolon, with consequent disturbance of sexual function during the course of the malady. Such sexual disturbance would certainly be attributed to the abdominoperineal rectosigmoidectomy unless the sexual antecedents of these patients are investigated.

We were not able to trace any connection, as some investigators claim to have done, between the height of the anastomosis and the maintenance of fecal continence, since in the cases in which it was made at a level considered optimum (6 cm.), fecal incontinence, although transitory, lasted for a longer period. In no case in our series was the anastomosis made at less than 3 centimeters, which fact makes it impossible for us to establish the maximum limit for resection of the rectum without prejudice to fecal continence.

SUMMARY

A study was made of the sexual activity and fecal continence in 40 patients with acquired megacolon after abdominoperineal rectosigmoidectomy.

The series is small for any definite conclusions, but the following facts became apparent:

1. Abdominoperineal resection of rectosigmoid has no adverse effect on most of these patients (31 cases).

2. Many patients who preoperatively suffered from reduction of the power of erection, the desire for intercourse, and reduction in sensory response, recovered full sexual activities after the operation.

3. Three patients with evident reduction in potency before the operation became permanently impotent after abdominoperineal resection of the rectosigmoid.

4. In 3 cases, decrease of seminal discharge evident before operation was not altered after it.

5. Only 1 patient with normal sexual activity before operation suffered loss of ejaculation and reduction of potency after abdominoperineal resection of rectosigmoid.

6. In 2 women with preoperative loss of desire for intercourse and of sensory response, this loss was not altered after operation.

7. The mechanism by which potency is reduced in the male or completely lost in the female in acquired megacolon is as yet unknown. It is possible that similar lesions of Auerbach's plexus of acquired megacolon may occur in the genital tract. This theory may explain the reduction of ejaculation before any operation in 3 patients. Even so, care must be taken to avoid any nerve injuries during abdominoperineal resection of rectosigmoid.

8. Fecal continence was normal in the immediate postoperative period in 32 patients —80 per cent. Eight patients presented temporary fecal incontinence for liquid stools for a period of 3 to 120 days.

9. No relation between fecal incontinence and the level of the anastomosis was present in this series.

10. Even anastomosis made at a level of 3 centimeters above the mucocutaneous line did not result in permanent incontinence.

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# RADIATION THERAPY OF CARCINOMA OF THE TONGUE

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THE TREATMENT of cancer of the tongue originally was limited to surgery. The development of radiation therapy during the last 3 decades and its application in the treatment of cancer of the tongue resulted in the improvement of end results with the avoidance of the mutilation associated with surgery. Radiation therapy, therefore, became more generally employed. However, progress in surgery facilitated by improved anesthesia, replacement of blood, control of infections, and the better training of surgeons in this field encouraged a trend to surgery again to such an extent that suggestions were made to abandon radiation therapy completely or restrict its use to palliation. Such recommendations do not take into consideration the fact that the most favorable results in surgery are obtained in relatively early lesions of limited extent. These superior achievements are then often unfairly compared with end results in patients who were rejected for surgery, either because of the advanced stage of the disease, the age of the patient, debility, or other complicating factors.

It therefore appears justifiable to report on a series of patients with carcinoma of the tongue who were treated mainly or exclusively by radiant energy. The majority of these patients had been seen by surgeons who believed for the reasons given that surgery was contraindicated. It is, therefore, not surprising that of the 86 patients reported here, only 10 had carcinomas which could be considered as early lesions.

Carcinoma of the tongue is the most common of all malignant lesions of the oral cavity, although there are considerable variations in the percentage figures reported in the literature. Some of these differences can be explained by analyzing the sources of the statistics, as, for example, whether they were compiled in general hospitals or institutions with prevailing specialization in cancer patients and therefore with a disproportionate percentage. Wookey and associates found that 40 per cent of all carcinomas in the oral cavity were localized in the tongue, whereas Cade (4) reported 69 per cent of cancers of the tongue in his group.

The disease is more frequent in men than in women, although again there is a considerable discrepancy in the figures of this relationship reported by various authors. Ackerman and del Regato found a relative incidence of only one-fifth to one-fourth, which indicates a percentage of 55 in men. Cade and Lee (5) reported a ratio of 66 per cent, Martin and coworkers (11) 87 per cent, and many other investigators a figure of 90 per cent and more in men as compared with women.

It is generally agreed that carcinoma of the tongue affects people of older age groups, predominately in the decade between age 60 and 70 years. Minor deviations have been reported, as for example, by Martin and coworkers (11) and Catlin who found the average age in their groups to be 58 years. Gibbel and associates, who reported on a group of patients who were all males, determined their average age to be only 52.6 years. With few exceptions, most investigators agree that carcinoma of the tongue develops in men at a more advanced age than in women, the difference being between 2 and 10 years. Braund and Martin observed that the younger patients had a higher incidence of distant metastases than patients in advanced age groups.

Of interest is the demonstrated frequency of syphilis in patients with cancer of the

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tongue and the implication of an etiologic relationship. Wookey and associates reported 8 per cent of syphilitics among their patients, Jacobsson reported 17 per cent, many others approximately 20 per cent, and Ackerman and del Regato 20 to 40 per cent. The importance of this relatively high incidence of syphilis as an etiologic factor is problematic, but it has some significance in the therapeutic response to radiation therapy.

More important as an etiologic possibility is pre-existing leucoplakia. Reports in the literature indicate that from 10 to 50 per cent of all patients with carcinoma of the tongue had leucoplakia prior to the development of the malignant lesion. The difficulty of establishing the transition from leucoplakia to carcinoma is emphasized and also the fact that the lesions may coexist. Our own observation indicates that the relationship of leucoplakia and cancer of the tongue appears to be more real than that of the two lesions in other parts of the oral cavity, notably the buccal mucous membrane and the soft palate.

The localization of carcinoma of the tongue is of great therapeutic and prognostic importance; it is generally agreed that lesions in the anterior two-thirds offer a more favorable prognosis. Catlin reports that in his group 50 per cent of the malignant tumors arose in the middle third, 33 per cent in the anterior third, and the remainder in the posterior third. Gibbel and associates, in a series restricted to male patients, found affliction of the posterior third to be 48 per cent. Russell reports that in his group cancer of the anterior portion of the tongue was 7.7 times as common as that originating in the posterior portion and that in males the incidence of posterior third lesions was 3 times greater than that of anterior lesions. It does not appear that any significant conclusions can be drawn from these observations.

The majority of malignant tumors of the tongue are squamous cell carcinomas. Cade and Lee (5) found that all but 8 of 653 patients showed squamous cell carcinoma; the exceptions included lymphoepithelioma, adenocarcinoma, and angiosarcoma. Gibbel and associates reported squamous cell carcinoma in more than 95 per cent of their patients, and a minimum percentage of 90 is reported in the literature. Martin and coworkers (11) distinguished between 90 per cent incidence of squamous cell carcinoma in the anterior two-thirds of the tongue and 80 per cent in the posterior third. This difference appears to be logical, considering the preponderance of lymphoid tissue present in the posterior third of the tongue.

The involvement of regional lymph nodes with carcinoma as the first sign of metastatic spread is of paramount importance for the prognosis and also influences to a considerable degree the form of therapy to be employed. A patient who would tolerate a hemiglossectomy or total glossectomy might be unable to undergo an additional dissection of the neck lymph nodes unilaterally or bilaterally. Shedd and associates described lymph node metastases in 37 per cent of their patients with anterior lesions, as compared with 71 per cent in the carcinomas of the posterior part of the tongue. The fact that carcinoma of the tongue in the posterior third is usually diagnosed when in a more advanced stage of the disease is one reason for the high incidence of lymph node involvement at the time of the first observation. Irrespective of the site of the primary carcinoma, the incidence of regional lymph node metastases reported in the literature varies between 39 per cent and approximately 70 per cent. In comparing end results from different sources, these findings must be given proper consideration.

Distant metastases to such sites as the larynx, esophagus, and lungs are infrequent and usually observed after spread to the regional lymph nodes. A range between 3 and 18 per cent is reported in the literature. Visceral metastases are relatively unusual, but their incidence is reported by Braund and Martin to be 2½ times greater in

patients with cervical lymph node involvement than in those not thus affected.

Until recently, most investigators agreed that with the possible exception of very early lesions of the tip of the tongue, where local excision can be successfully employed, the treatment of choice of the primary carcinoma of the tongue is radiation therapy in one or more of its various applications. The present claim of surgeons that, with improved surgical methods, results superior to those of radiation therapy have been and will be achieved has yet to be substantiated within the next years, when an increasing number of patients treated by surgery can be studied. This is also true for the recommendation of complete resection of the involved tongue in continuity with the ipsilateral metastatic lymph nodes, when these are enlarged, as advocated by Shedd and coworkers. Catlin recommends surgery for small lesions of the anterior two-thirds of the tongue, stating that the results of radiation therapy in this area are not better than those of surgery. Reports of experience with radiation therapy are, therefore, important for comparative purposes. The factors to be considered in evaluation of different methods are not restricted to the stage of the disease alone but must include the type of radiation therapy and the skill with which it is executed. This necessity is best illustrated by comparing the therapeutic results of patients treated in institutions in which experience has been acquired through diligent efforts of individuals and a tradition of effective management has been developed and the survival rates in hospitals or offices where radiation treatments are carried out as an adjunct to diagnostic radiology and where supervision and execution of radiation therapy are often delegated to the junior members of the staff or to technicians.

Modalities used for radiation therapy by various investigators included (1) roentgen rays in the range of 200 kilovolts to 1 to 2 million volts, (2) radium in the form of surface applicators, (3) insertion of radon seeds or radium element in removable needles, (4) radium in greater quantities in so-called bombs as telecurietherapy, and (5) cobalt 60 as a convenient and less expensive substitute for radium, mainly in cobalt 60 bombs. The judicious choice of any one of these modalities may determine the success or failure of radiation therapy.

Although orthovoltage roentgen ray therapy has been utilized in the treatment of carcinoma of the tongue, reports in the literature indicate that the end results of using radium in its different forms, cobalt 60, or roentgen rays in the 1 to 2 million volt range are definitely superior.

Generally, telecurietherapy with radium bombs, recently replaced by cobalt 60, in combination with radium implantation has been the preferred method of treatment in European centers. In the United States supervoltage roentgen ray therapy or cobalt 60 with or without interstitial radium is presently favored.

Berven and Jacobsson at the Radiumhemmet in Stockholm treated the primary tumor and cervical metastases when present by means of radium bombs and observed no additional benefits from local radium implantation; only when after completion of telecurietherapy a residual tumor remained did they employ interstitial radium or electrocoagulation. Wood of Hammersmith Hospital in London preferred telecurietherapy with a radium bomb. Windeyer treated anterior lesions with interstitial radium and posterior lesions with telecurietherapy. A similar attitude was taken by Cade and Lee (5); they recommended that telecurietherapy be reserved for inaccessible tumors and that surgery be employed only for recurrent lesions. Martin and Martin (10) in this country recommended radium implantations for almost all cancers of the tongue and reported some of the highest 5 year survival rates. Similar favorable results have been obtained by Wookey and associates who employed roentgen rays of 200 to 400 kilovolts in combination with radium implantation and

surgery, the latter being recommended mainly for metastases in the cervical lymph nodes. Marchetta and Mattick also utilized roentgen rays for intraoral treatments and orthovoltage radiation for metastases of the cervical lymph nodes; their 5 year survival rates are lower than those reported by most. Interstitial radium in combination with roentgen rays were used by Shedd and associates. The 5 year survival rates in percentage figures for the series of the authors mentioned are: Berven and Jacobsson, 28; Wood, 26; Windeyer, 21; Cade and Lee, 24; Martin and Martin, 33; Wookey and associates, 33; Marchetta and Mattick, 17; and Shedd and associates, 20.

It is not possible to draw specific conclusions from differences in these survival figures, since the end results do not depend solely on the method of treatment or on the skill of the radiotherapist; they are greatly influenced by the localization of the primary tumor, the extent of the disease, the involvement of the regional lymph nodes, and the presence of distant metastases. Variation of these factors in the reported series of patients makes a comparison impracticable. However, the assumption that properly executed radiation therapy should control at least 20 per cent and possibly as many as 25 to 30 per cent of all cancers of the tongue for 5 years appears to be justified. One of the factors which adversely influences the attainment of higher survival rates is the predominance of posterior lesions in the groups of reported patients. There is general agreement that the localization of the primary tumor greatly influences the patient's prognosis. Berven and Jacobsson, whose average 5 year survival figures are 28 per cent, reported that of their patients with anterior lesions 30 per cent lived, whereas of those with posterior lesions only 12 per cent survived. Windeyer, with a 21 per cent average survival rate, reported almost 30 per cent for anterior lesions and less than 10 per cent for posterior tumors. Martin and associates (11) considered the outlook for survival of patients with posterior lesions to be only one-third that of those with anterior tumors. Cade and Lee (5) reported 35 per cent survival of patients with tumors in the anterior two-thirds of the tongue and 11 per cent in those with posterior primary lesions. A notable exception to these reports was published by Martin and Martin (10) who, with an over-all survival rate of 33 per cent, found 38 per cent 5 year survival rates in patients with primary tumors in the posterior third. A possible explanation of this discrepancy may be that relatively early lesions were encountered in the published series in which more than 50 per cent of the patients were found to be free of metastases to the cervical lymph nodes at the time of treatment.

The presence of metastatic spread to the regional lymph nodes reduces the cure rate drastically regardless of the methods of treatment. As an example, Martin and coworkers (11) reported 34 per cent survival rates over a period of 5 years in patients without lymph node involvement and only 8 per cent in the presence of metastases. Patterson's corresponding figures are 41 and 8 per cent; Jacobsson's, 52 and 15 per cent; Wood's, 35 and 17 per cent; and Cade's and Lee's, 51 and 14 per cent. From these reports it is obvious that improvement in survival rates can be expected only when patients are properly treated in an early stage before metastases have occurred and after the development of better methods for the control of lymph node metastases, once these have occurred.

Theoretically, a good case can be made for the performance of prophylactic dissection of the neck lymph nodes in all instances of carcinoma of the tongue, and indeed this has been advocated by a number of investigators. Whether such radical procedures are justified will be discussed later.

Our own experience is based on 86 patients observed from 1938 to 1953, inclusive. The mean age of these patients was 61 years, with an extreme range between 26 and 86 years. The general observation of earlier development of carcinoma of the

tongue in women was confirmed in this series: the mean age of women being 56 years and that of males 63 years. Of the 86 patients in this group, 4 (4.7 per cent) had a history of previous infections with syphilis and only 1 of these had clinical evidence of syphilis in the tongue. The incidence of preexisting or coexisting leucoplakia was observed in 12 (14 per cent) of our patients. In 84 patients, a diagnosis of squamous cell carcinomas with varying grades of malignity was made; in the other 2, an adenocarcinoma and a lymphoepithelioma were diagnosed. The prevalance of squamous cell carcinoma is in accord with findings of other investigators, although the relatively large numbers of carcinomas originating in the posterior third of the tongue in our group might theoretically have favored a larger number of other histologic forms of the primary tumor. The site of the origin of the primary lesions was fairly evenly divided. There were 27 carcinomas in the anterior third, 29 in the middle third, and 30 in the posterior third. A striking difference was observed in the localization of the primary tumors between the sexes. In the group of anterior third lesions, the ratio between men and women was 17 to 10; in the middle third, 23 to 6; and in the posterior third, 28 to 2.

Considering the primary site of the tumor in relation to the development of metastases, only one-third of the patients with carcinoma in the anterior third of the tongue had lymph node involvement at the initial examination; 62 per cent of the primary lesions in the middle third showed metastatic spread to the lymph nodes; and 70 per cent of the primary carcinomas of the posterior third had developed metastases. In 7 patients (8 per cent) metastases developed to such distant organs as the larynx, esophagus, and lungs.

With the exception of 2 patients who refused therapy for personal reasons, treatments were carried out by telecurietherapy with or without interstitial radium. Of the total group of 84 treated patients, 10 received only radium implants; 8 of these had early lesions in the anterior two-thirds of the tongue without local extension or metastatic spread; 2 had posterior tumors. The prognosis in these 10 patients was considered to be favorable; however, the follow-up in 4 of this group was poor, mainly because these patients, being unaware of the seriousness of their disease, were tardy or indifferent to periodic examinations and eventually were untraceable. One of these patients died 16 months after therapy from unrelated causes and free from evidence of cancer. The remaining 3 were free from symptoms when last examined, 7, 16, and 38 months, respectively, after treatment. For statistical evaluation, these 4 patients are considered to be dead from the disease.

Of the remaining 74 patients, 14 received telecurietherapy as the only form of treatment. All of these patients had bilateral metastases to the lymph nodes of the neck when first observed, and treatments were given as a palliative measure. Fifty-six patients received combined therapy. In a few instances intraoral roentgen ray therapy was added as a therapeutic measure, and 1 patient had a local surgical excision.

Table I shows the location of the primary tumors in the tongue, indicates whether or not lymph node involvement was present at

TABLE I.—DATA ON PATIENTS SURVIVING A MINIMUM OF 5 YEARS AFTER RADIATION THERAPY

| *Site of primary tumor* | *No. of patients* | *Survival minimum 5 years* | *Lost to follow-up* | *Per cent 5 year survival* |
|---|---|---|---|---|
| Anterior third/total | 27 | 9 | 5 | 33 |
| Without lymph node involvement | 18 | 7 | | |
| With lymph node involvement | 9 | 2 | | |
| Middle third | 27* | 5 | 8 | 18.8 |
| Without lymph node involvement | 11 | 3 | | |
| With lymph node involvement | 16 | 2 | | |
| Posterior third | 30 | 6 | 11 | 20 |
| Without lymph node involvement | 10 | 2 | | |
| With lymph node involvement | 20 | 4 | | |

Without lymph node involvement—survival 30.7 per cent.
With lymph node involvement—survival 17.7 per cent.
Lost to follow-up examinations—28.5 per cent.

*The 2 patients not treated were in this group.

the time of treatment, tabulates the survival time without symptoms for a minimum period of 5 years, and reveals the relatively high number of patients lost to follow-up (28.5 per cent). The survival rates are highest in the group with primary lesions in the anterior third of the tongue (33 per cent), and they are almost identical in the groups with lesions of the middle and posterior third (18.8 per cent and 20 per cent, respectively). The over-all salvage rates of the 84 treated patients is 23.8 per cent. Apparently, the presence or absence of lymph node metastases at the time of therapy is prognostically more important than the localization of the primary tumor. Of those patients who seemed to be free of metastases, 30.7 per cent lived 5 years without symptoms, whereas the presence of lymph node involvement reduced the 5 year survival rate to 17 per cent. An indicator of the advanced stage of the disease at the time of therapy in this group is found in the observation that, of the 84 patients treated, 15 (17.8 per cent) died within a year after termination of therapy.

Our treatments consisted of radium in the form of telecurietherapy with a 4 gram bomb and/or implantation of radium in the form of low intensity needles. As mentioned before, a small group of patients (11 per cent) were treated with interstitial radiation only; of the patients with advanced lesions, 16 per cent were treated with telecurietherapy only. With the exception of these latter patients who were treated for palliative purposes only, the minimum amount of radiation administered to all other patients was 6,000 to 7,000 gamma roentgens to the primary tumor. Although many such factors as infection, age of patients, concurrent diseases, and presence of metastases influenced the treatment plans in individual instances, our initial therapeutic effort was directed at the primary tumor with the intention of avoiding or blocking metastatic spread during therapy which generally lasted over a period of 5 to 6 weeks.

The clinical disappearance of the primary tumor, although a *conditio sine qua non* in the treatment of all malignant tumors, is no guarantee that the neoplasm is controlled. An effort must be made to treat effectively the regional lymph nodes, certainly a compelling factor in our series in which the incidence of metastatic spread at the time of first consultation was 56 per cent. Contrary to the present prevailing concept of surgical treatment of lymph node involvement by unilateral or bilateral radical dissections of the lymph nodes in the neck, none of the patients reported here were subjected to surgery. One reason is that this survey dates back to 1938 when surgical procedures of this type were less popular and less successful. Another reason is that these patients responded well to intensive telecurietherapy which was routinely employed in all instances with the exception of 10 patients (less than 12 per cent) in whom small tumors were treated with local radium implantation only. Treatments were routinely started with telecurietherapy, and the beam, aimed from the outside at the primary tumor, always included the regional lymph nodes whether or not they were involved with metastatic spread. Many of the patients so treated who had histologically proved lymph node involvement are in the group of 5 and more years' survival, and we believe that the adequacy and effectiveness of radiation therapy have been confirmed in these instances. However, in the last few years, radical dissections of metastatic lymph nodes of the neck were performed in patients in whom the operation did not present a risk. Our recommendations with regard to radical surgery are mainly influenced by the extent of the metastases, the age or debility of the patient, and such other complicating factors as concurrent systemic diseases which might increase the surgical risk. None of the patients who had radical dissections of the lymph nodes of the neck are in the group here reported, and an evaluation as to whether better end results can be achieved with such combined therapy does not seem appropriate at this time.

A different problem is whether all patients with primary carcinomas of the tongue should undergo a prophylactic dissection of the cervical lymph nodes. Although it may be justified to assume that a tumor which has been in existence for many months has produced metastases to the regional lymph nodes, the actual occurrence can be proved only after microscopic examination. There is no doubt that early invasion of the lymph nodes, which is often not clinically manifest, can be controlled by radiation in the described manner. The inclusion of the regional lymph nodes in the treatment fields and the application of a cancericidal dose to the node-bearing area should result in the control of metastases. The same expectations are not valid for surgical excisions of primary carcinomas of the tongue. The removal of a tumor that has produced metastases implies cutting through tissue afflicted with active neoplasm, and such surgery should logically be supplemented by lymph node dissections or radiation therapy which may control any possible implantation or spread by the original surgical procedure. Therefore, the attitude after a primary approach by surgery should be different from that after radiation. In the first instance, the reasons for prophylactic neck dissections appear to be compellent; in the latter instance, the indications are questionable and probably unnecessary.

This report is an attempt to evaluate the results of radiation therapy in the management of cancer of the tongue and to establish a base for comparison with results achieved by surgery alone. It has been rightfully claimed and acknowledged that, in the last decade, surgical procedures have been considerably improved and that surgical skill of individuals has developed far beyond the status prevalent only a decade ago. However, it must be conceded that the facilities and methods of radiation therapy have been also immensely improved and that many more well trained radiotherapists are now available who are familiar with cancer therapy. The introduction of high voltage roentgen ray equipment in the 1 to 2 million volt range and the availability of cobalt 60 as an inexpensive substitute for radium have contributed to treatment potentialities in a field in which orthovoltage roentgen ray therapy admittedly is not adequate. Furthermore, whereas 20 years ago in the United States not more than 6 radiologists devoted their efforts exclusively to therapy, there are now more than 100 specialists who limit their work to the therapeutic aspects of radiology. It seems reasonable, therefore, to expect that results heretofore achieved in only a few centers can be duplicated and improved upon.

It has been stated that, at present, the 5 year survivals after radiation therapy of carcinoma of the tongue range between 20 and 30 per cent in the large centers, and one may safely assume that the over-all average survivals in the country are much less favorable. The solution of the problem of improving these survival figures is difficult but does not appear insurmountable. The first consideration must be given to the establishment of an earlier diagnosis. This factor is, of course, not specific for carcinoma of the tongue but holds true for all malignant lesions. Although we do not subscribe to the absolute validity of the slogan "early cancer is curable," since many primary carcinomas of the bronchus or the breast do not follow such a simple pattern, this factor seems to be of deciding influence in dealing with carcinoma of the oral cavity and especially of the tongue. Educational efforts in this field are not only valuable but also have already proved to be rewarding. An analysis of our own figures is significant: If we were to exclude the 18 patients who received radiation therapy for palliative purposes only and were not treated with a cancericidal dosage, our 5 year end results would improve from 23 per cent to 30 per cent. Our experience during the last few years indicates that the group of inoperable and far advanced carcinomas of the tongue has been represented in a smaller percent-

age of the total number; this alone should result in higher 5 year survival figures even if there were no improvement in present treatment methods.

Another important consideration is the choice of the treatment method at the time the patient is first seen. In the past, surgeons undoubtedly have been called upon to operate on primary carcinomas of the tongue which had not been controlled by radiation therapy or had been shown to be "radioresistant." It is very probable that the treatments in many such "radioresistant" cases were either wholly inadequate or not carried out with sufficient skill. In the last few years we have observed a reverse trend: patients treated with extensive surgery including total or hemiglossectomy, resection of large segments of the mandible, and dissection of the neck lymph nodes were referred for radiation therapy because recurrences had developed at the edges of the surgical scars within a few months after the procedures. In such instances, the patients were either not good candidates for surgery in the first place, because of the histologic type of tumor—usually highly anaplastic squamous cell carcinomas—or the wide and mutilating surgery was still not sufficient to control the extensive tumor involvement. Soundness of judgment should include the careful consideration of the sequelae of such major surgery. The fact that an operation is technically feasible is not necessarily a logical reason for choosing surgery when an alternative and less mutilating treatment is available and equally successful. The final evaluation of the two different therapeutic approaches will require more study and considered judgment. It is our belief that unless the now advocated radical surgical treatment of carcinoma of the tongue shows unqualified superiority as expressed in considerably higher 5 year survival figures, it should not replace radiation therapy.

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# CORONARY BLOOD FLOW MEASURED BY A SURFACE COUNTING TECHNIQUE

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IN A STUDY of the cardiac output as it is recorded by surface counting, it was stated that an expression for coronary blood flow could be obtained by measuring the area of a third peak appearing on the downslope of the peak representing the flow through the left chambers of the heart (2, 3). This third peak appears simultaneously with the appearance of the radioactivity in the circulation of the neck. The original hypothesis was that the peak represented the peripheral circulation in the heart region and that the peak was not distorted by early recirculation of the tracer dose. However, even though estimates of coronary blood flow made from the area of this peak agreed adequately with standard methods, it was still possible that this peak contained recirculation of the tracer bolus. Recirculation of the coronaries from the relatively short vascular circuit might appear early enough to be included in this peak. In addition, since the mediastinal blood vessels and the aorta were within range of the detector, the recorded curve might be relatively too large since it would contain radioactivity in these blood vessels as well as in the heart. In order to answer these questions, experiments were performed with the tracer bolus temporarily excluded from the coronary circulation of dogs. In addition, records obtained from patients free of cardiovascular disease were reviewed in order to determine the mean time for the radioactive bolus to reach the coronary circulation and also the mean transit time of the bolus through the coronary circulation.

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## METHODS

*Dog experiments.* The detecting equipment consisted of a scintillation tube with a 2 inch sodium iodide crystal surrounded by a 1 inch thick lead shield without collimation but with a ⅛ inch thick lead filter on the face of the crystal. This detector was placed over the exposed dog heart. Impulses from the detector were fed into a ratemeter with a 0.1 second time delay and registered on a rectilinear recorder. The total deflection on the recorder represented 25,000 counts per minute. A tracer dose of 0.1 to 0.2 milliliter of radioactive diodrast containing 5 to 10 microcuries of iodine ($I^{131}$) was used. The recording equipment remained unchanged throughout. After pentothal anesthesia, the chest wall was opened with a transsternal incision through the fourth or fifth interspace. Both right and left coronary arteries were dissected free from the myocardium proximal to their first branch. A silk ligature was placed around each coronary artery, and the two ends were passed through a short piece of rubber tubing. The coronary arteries could then be temporarily occluded by drawing them against the rubber tube (Fig. 1). A thin catheter was passed into the superior vena cava via the jugular vein. After the tracer bolus was injected into this catheter, it was forced into the circulation by rapidly injecting 5 milliliters of saline. Occlusion of the coronaries was accomplished only after the tracer bolus had passed into the right chambers of the heart as registered by the first radioactive peak on the recording. No change in pulse rate occurred dur-

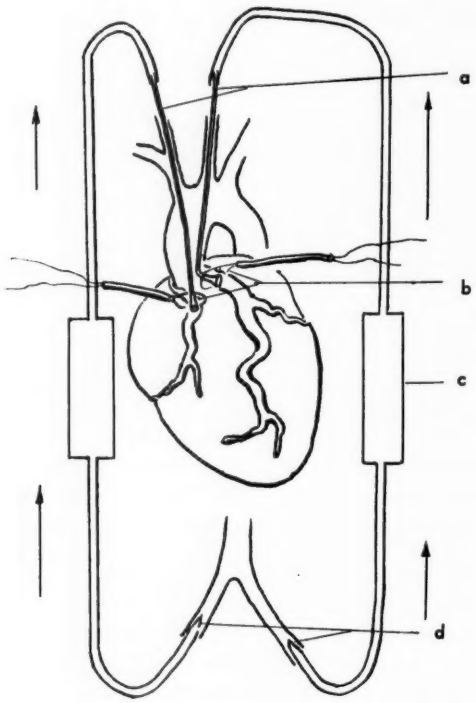


FIG. 1. Diagram of procedure. *a*, Brass cannulas inserted into right and left coronary arteries via coronary ostia. *b*, String running through a rubber tubing and looped around both coronary artery roots. *c*, Reservoir. *d*, Cannulas in femoral arteries.

ing the few seconds required by the bolus to pass through the left chambers of the heart. As soon as the radioactive bolus had passed the heart and coronary bed as shown on the recording, the coronary arteries were released.

In separate experiments, the coronary arteries were perfused from a peripheral arterial source. This perfusion was accomplished by passing specially constructed brass catheters through each carotid artery into the aorta. The curved end of the tube catheter was placed into each coronary ostium (Fig. 1). The ligatures already in place around the arteries were secured around the tubes. These cannulas supplied the myocardium with the blood from a peripheral arterial source. In this way, the coronaries remained free of radioactivity long enough to allow the radioactive bolus to clear the heart completely before returning to the coronary circulation.

*Human experiments.* The technique used in the human experiments was identical to that already reported (2). In order to obtain the mean value for the length of time which elapses between the start of the cardiac peak and the coronary peak we measured this distance on 60 consecutive records obtained from patients deemed to be free of cardiac disease by routine clinical examination. In addition, the mean distance between the start of the coronary peak and the point where recirculation first begins was also measured. These curves were recorded at the rate of 12 inches per minute and the measured distances were converted to seconds so that these data could be compared to similar values in the literature. A typical curve is shown in Figure 2. The two distances are shown on this curve labeled $PT_c$ and $PT_h$.

## RESULTS

Characteristic recordings from the dog experiments are shown in Figures 3 and 4. The upper tracing in each figure represents a control curve. The control curve was run before the coronary circulation was separated from the general circulation. On each of these curves two major peaks are recognized. The one appearing first along the time axis represents the circulation of the right chambers of the heart. The second peak is produced by the tracer passing through the left chambers of the heart. On the downslope of the left side of the heart another and smaller peak appears. In each of 8 experiments when the coronary circulation was occluded during passage of the radioactive bolus, this convexity or coronary peak completely disappeared. Typical examples of these results obtained are shown in the middle curve of Figures 3 and 4. The downslope of the left ventricle curve is shown to be concave along its course.

A similar curve was obtained during the

time that the coronary vessels were perfused by an extra-aortic blood source which had been separated from the first circulation of the tracer bolus by delaying passage of the radioactivity in two vessels connected to the circulation. These are the lower curves in Figures 3 and 4. It can be observed that the area of the cardiac curve in the lower curve is increased over the area of the other two curves. This resulted from the gradual decrease in cardiac output produced by the prolonged manipulation of the heart during these last experiments. Again, no coronary peak is demonstrable. The recirculation peak appeared much later than the coronary peak and only after the left ventricular peak had reached a very low value. The early recirculation peak seen with intact coronary flow in the control curves must represent coronary recirculation since it is not seen when the coronary arteries are temporarily separated from blood containing the tracer bolus.

In order to prove this, the mean transit time and coronary recirculation time were measured on records obtained from patients free of cardiovascular disease. The mean time for the radioactive bolus to pass from the beginning of the heart curve to the start of the coronary peak was $11.1 \pm 0.3$ seconds (mean $\pm$ standard error of the mean) in 60 consecutive curves. The sample range was 7 to 12 seconds. The mean duration of the visible portion of the coronary peak from its start to the beginning of recirculation was $4.3 \pm 0.1$ seconds. The sample range was 3 to 8 seconds. These values compare favorably with those in the literature.

## DISCUSSION

Comparing all curves, it is obvious that in each experiment when the coronary circulation was separated from the general circulation a third peak is not seen on the downslope of the left ventricular peak. The original hypothesis was that the third peak represented peripheral circulation in the heart region and that the coronary circulation constituted a major portion of it. In all the

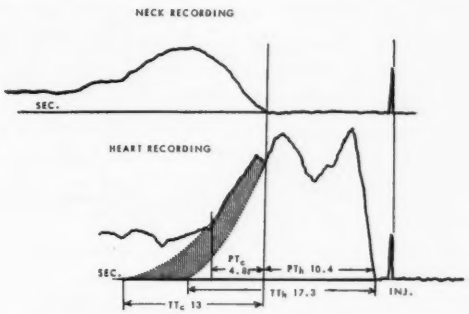


FIG. 2. Time activity curve obtained from a normal patient. $PT_h$ is the time it takes the leading edge of the radioactive bolus to pass through the heart. $PT_c$ is the similar time for the coronary circulation.

curves where no radioactivity passes through the coronary circulation, the third peak does not appear, despite the fact that mediastinal blood vessels and the aorta contain radioactivity and are within the range of the sensitive area of the detector. These blood containing organs do not produce a significant deflection on the time activity curve because we have found that deflections are more dependent on the amount of the radioactivity seen at any one time than on the total amount of radioactivity passing the detector (4). At any one moment too little radioactivity is in the aorta and in the mediastinal blood vessels to produce a significant deflection on the graph. However, the myocardial capillary bed does contain enough blood to accumulate sufficient radioactivity within the range of the detector to produce a deflection. The coronary capillary bed is the only large capillary bed in this area.

Blood traversing the coronary circulation has one of the shortest circulation times in the body. It is possible that the third peak might portray the return of a portion of the tracer bolus to the right chambers of the heart via the coronary circulation. In this way the third peak would still be related to coronary blood flow. We believe that this peak represents coronary capillary flow and not the first recirculation, because the appearance time of the third peak is simultaneous with the appearance time of radioac-

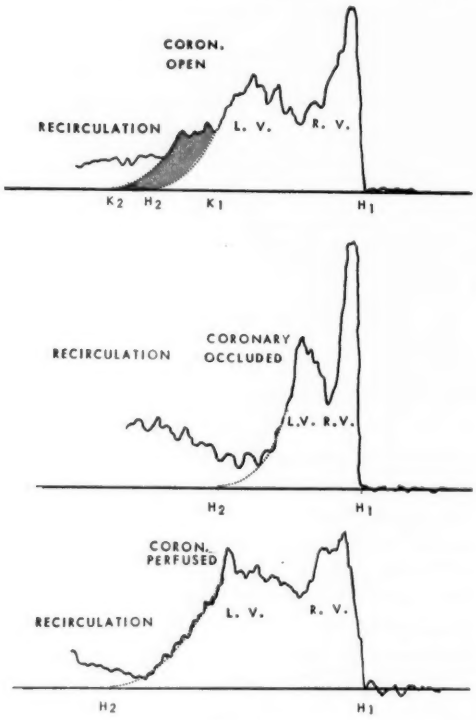


FIG. 3.

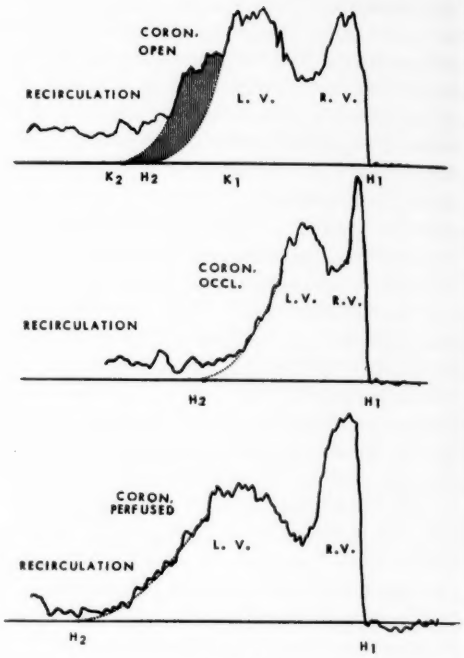


FIG. 4.

FIGS. 3 and 4. Characteristic recordings from the dog experiments.

tivity in other nearby peripheral circulations, i.e., neck muscles or kidney. Coronary transit time has been reported by Waser and Hunguyer to be at least 5 seconds, which is longer than the time it takes blood to reach the neck and kidneys.

Crane and associates studied the circulation time of radioactivity in the human. In 19 patients they noted that a bolus injected into the right atrium took about 11.7 seconds to reach the brachial artery. A similar mean transit time of $11.1 \pm 0.3$ seconds was found in 60 determinations of this time from our data. This finding again suggests that the third peak appears too early to represent recirculation of the tracer bolus. They also noted that the earliest recirculation appears in the right ventricle on the average $4.4 \pm 3.4$ seconds after the radioactivity first appears in the brachial artery. This would mean a coronary peak greater than 4.4 seconds in duration could contain its own recirculation. Checking back over 60 curves, we found that the mean length of the visible, not extrapolated, part of the coronary peak by our method is $4.3 \pm 0.1$ seconds, indicating that probably it is not distorted by its recirculation.

Surface counting technique for determining of cardiac output had been in use for several years before the coronary peak was noted. Depending upon where the extrapolation was started, investigators may have included the coronary peak in their cardiac output curves monitored at the chest wall. Yet, some investigations were able to obtain values which in most cases compared favorably with the direct Fick procedure. At least some of these extrapolated curves must have contained the coronary peak and in-

deed it can be seen in some of the curves in the literature. Including the area of the coronary peak obviously would give too large a heart area and, in this way, result in too low a value for cardiac output. However, since the equilibrium reading includes blood in the heart chambers as well as that in the myocardium, this is relatively too large also and in this way it must compensate adequately for the increase in the area of the heart curve.

SUMMARY

The time activity curve registered precordially has been shown to be composed of three separate peaks. The first two of these peaks represents the passage of the radioactive bolus through the right and left chambers of the heart. The third of these three peaks appears to represent coronary circulation. The evidence for this is that this peak is not present when the radioactive tracer bolus is excluded from the coronary circulation, that on the average this peak starts simultaneously with the appearance of the radioactivity in the peripheral circulation, and that on the average this peak ends before the beginning of the earliest recirculation of the tracer bolus.

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# EDITORIAL

## THE DIAGNOSTIC LAPAROTOMY

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A LAPAROTOMY undertaken without effort to make a diagnosis beforehand is looked upon with disfavor; this is proper. Yet a clinical discipline too strict in its dependency on roentgenography and chemistry may dangerously put off the direct course offered by a diagnostic laparotomy. Sometimes this operation is delayed until everything else has been tried and the patient's funds, patience, and chance of cure have all been sadly diminished. Laparotomy for diagnosis deserves earlier, more frequent use and greater respect.

Unfortunately, reasons not concerned with the best interest of the patient may weigh against the use of a diagnostic laparotomy. An exploration revealing no pathologic condition may, for example, embarrass both the referring physician and the surgeon because it testifies to their lack of diagnostic acumen. The surgeon may fear further embarrassment because he believes that he has performed an unnecessary operation and will be accused of this. Vanity and lack of confidence may take precedence over the patient's welfare. If the laparotomy discloses a disease-free abdomen, the patient makes no criticism; he is relieved to have the matter settled.

An influence clearly concerned with the best interests of the patient, rather than with the doctor's embarrassment, which may delay laparotomy is that of operative risk. If the operation is dangerous it should be avoided. A laparotomy alone, however, in which no major resections are required, has a low risk. A few years ago I participated in a number of re-explorations or "second-look" operations for abdominal cancer. Among patients in whom no cancer was found at the re-exploration there were no deaths, even though most of the operations were in elderly patients and all required a thorough search in an abdomen thick with adhesions. These patients usually left the hospital about a week after the operation. The risk of a modern abdominal exploration is low.

In fact, the risk of an exploratory laparotomy is probably less than that of an exploratory thoracotomy. Despite this fact a diagnostic thoracotomy would appear to be more acceptable today, possibly because its use follows demonstration of an objective sign—a roentgenologic shadow. The futility of extensive preoperative diagnostic tests in pulmonary coin lesions is now recognized. Findings which may lead to a laparotomy, such as pain, indigestion, ill-defined masses, or chronic "flu," are vague in comparison to an x-ray shadow, but still sufficient for the responsible surgeon.

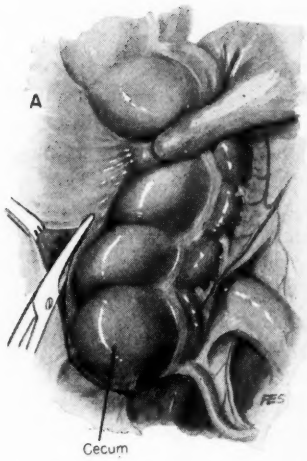
When a diagnostic exploratory laparotomy is undertaken it should be done by a qualified surgeon. As a surgeon should not undertake an appendectomy unless he is able to perform a colectomy, he should not undertake a diagnostic laparotomy unless he is competent to perform a pancreatectomy or resect an aortic aneurysm.

A diagnostic laparotomy does not always have to be a general abdominal exploration,

but it should be adequate for the specific case. In jaundice of doubtful cause, for example, a 2 inch incision that merely allows biopsy of the liver is not enough. The incision should be made twice as long so that the gallbladder and the common duct can be palpated. This is the quickest way of differentiating jaundice amenable to surgery from medical jaundice. If stones are found, definitive treatment can be undertaken immediately. If not, a 4 inch subcostal incision heals about as well as a 2 inch incision.

In addition to having wide technical competence, the surgeon undertaking a diagnostic laparotomy must also be able to reach a decision at the operating table concerning the best course. The responsibility is difficult. Yet, the expense of such an operation for the patient, particularly if no complex surgery is required, should not be great. If the expense is considerable, the procedure will be shunned by referring clinicians and there will be detrimental delay. To a considerable degree, this responsibility is the surgeon's. If the operation turns out to be merely an exploration, hospitalization should be short and the surgical fee should not be large.

There are pitfalls. The surgeon must avoid magnification of minor or insignificant pathologic conditions. If the exploratory findings are negative, he must admit this, both to the patient and to himself. It is enough, in such a case, if serious intra-abdominal disease has been ruled out. Fortunately, one hears little now of the dropped kidney, or of the retroverted uterus, or of chronic appendicitis, but the surgeon must also avoid attributing symptoms to nonobstructing adhesions, duodenal diverticula, or small cysts. The surgeon must be wary of the psychoneurotic. He cannot avoid all of these people for they may need surgery—even a diagnostic laparotomy—but indications must be strong. The deterring effect of laparotomy scars is traditional and sound.



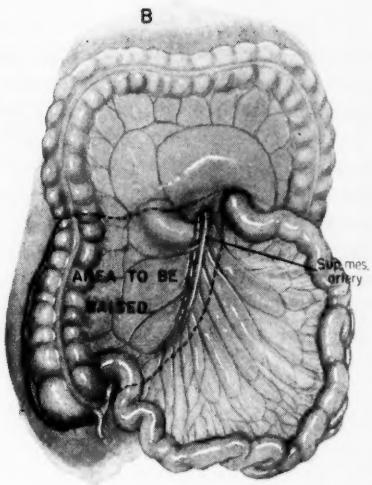




FIG. 1.

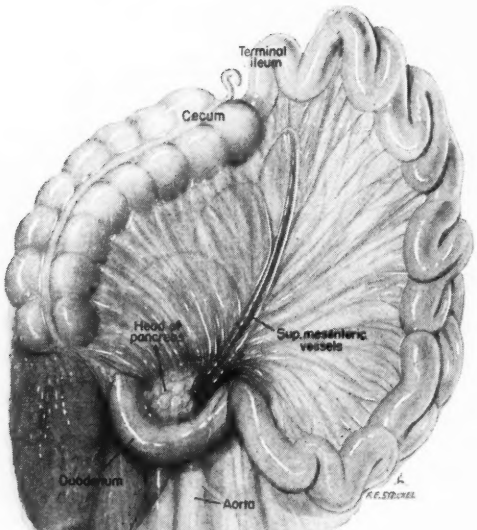



FIG. 2.

FIG. 1. Initial dissection for mobilization of the right side of the colon, small intestine, and mesentery.

FIG. 2. Exposure obtained of the third and fourth portions of the duodenum.

*A Technique for the Exposure of the Third and Fourth Portions of the Duodenum.—Richard B. Cattell and John W. Braasch.*

# THE SURGEON AT WORK

## A TECHNIQUE FOR THE EXPOSURE OF THE THIRD AND FOURTH PORTIONS OF THE DUODENUM

RICHARD B. CATTELL, M.D., F.A.C.S., and JOHN W. BRAASCH, M.D., F.A.C.S.,
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OCCASIONALLY one is confronted with the necessity for surgical management of lesions of the third and fourth portions of the duodenum. Exposure of this area is limited by the overlying mesentery of the small bowel and transverse colon with its superior mesenteric artery, vein, and branches. The technique to be described has been useful in obtaining direct access to this portion of the duodenum.

Certain changes occur in the embryologic development of the midgut and its arterial supply between the eleventh and thirteenth weeks of fetal life. This portion of the intestine rotates about the superior mesenteric artery as an axis, with final fusion of the mesentery of the right half of the colon to the posterior parietes. This technique for the exposure of the duodenum is based on raising the mesentery of the small bowel and right half of the colon along this line of fusion. As shown in Figure 1, the initial dissection is started by severing the lateral attachments of the cecum and right half of the colon. This line of cleavage is developed, raising the right half of the colon and the mesentery of the small intestine along with the superior mesenteric artery and vein. Figure 2 depicts the complete exposure obtained of the third and fourth portions of the duodenum after the ileum and right half of the colon have been mobilized completely. If resection of portions of the duodenum is required, the surgeon must safeguard the short branches of the first portion of the superior mesenteric artery which supply the proximal portion of the jejunum. For this reason, any dissection for removal of portions of the duodenum should be performed close to the duodenal wall.

To our knowledge, the only comment that has appeared in the literature on this approach to these lesions was in a discussion at a meeting of the Southern Surgical Association.[1]

This method was applied in a patient operated upon in July 1958. A roentgenologic study of the upper gastrointestinal tract revealed a polypoid tumor involving the third portion of the duodenum. This was verified upon exposure at operation. The third portion of the duodenum was resected and gastrointestinal continuity was reestablished by end-to-end anastomosis. The right half of the colon and the small intestine were replaced in their normal position within the abdominal cavity. No effort was made to resuture the right half of the colon to its normal attachments. Postoperatively, the patient's gastrointestinal tract has functioned normally.

This maneuver for exposure and direct visualization has been found useful in dealing with neoplasm, ulceration, or perforation occurring in the third and fourth portions of the duodenum.

From the Department of Surgery, The Lahey Clinic, Boston.

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# A SIMPLE NEW METHOD TO MAINTAIN ABDUCTION AT THE HIP DURING TRACTION

AMIN RIDA, M.Ch. Orth., Alexandria, United Arab Republic

WHEN TRACTION IS APPLIED to the lower limb for any traumatic or pathologic lesion in the region of the hip, abduction of the hip is usually very difficult to maintain; if the adductor muscles are in spasm and hip abduction is attempted, the patient's trunk usually follows the lower limb, the desired position cannot, therefore, be maintained, and the patient may actually fall from the bed.

It is an evident mechanical rule that when a force is applied to the lower limb in a certain direction an equivalent force has to be applied to the pelvis in the opposite direction so as to bring about the required effect. This is why traction cannot be effective without countertraction. If, during traction, the hip is flexed, a counterflexion force in the form of pressure on the patient's back is provided by the couch or the bed. When extension is needed, an opposing force applied to the patient's pelvis in a backward direction is secured by the weight of the patient's trunk. When abduction of the lower limb is aimed at, a counterabduction force should be applied to the pelvis in order to ensure the abduction. The following method is a simple one.

## METHOD

*Principle.* With the present method, fixed or balanced traction may be employed with any kind of splints in current use. The only new procedure introduced is raising the bed on the side of the leg under traction, so that when the latter is abducted the patient's pelvis does not follow it. The counterabduction force is produced by the patient's trunk gliding transversely away from the abducted leg (Fig. 1a). This can be compared, but in a different direction, to the usual longitudinal countertraction produced by raising the foot of the bed (Fig. 1b). If the bed is tilted and its foot raised at the same time, the lowest part of the bed will be the angle opposite the traction and the resultant direction to which the trunk glides is diagonal (Fig. 1c), producing both countertraction and counterabduction effects. This latter procedure is the basis of the following technique.

*Technique.* The foot of the bed is raised on wooden steps, higher on the side of the lower limb in traction; a wooden block to the height of the uptilted bed leg is placed under the bedpost on the headside. The degree of tilting is proportionate to the degree of abduction required. In fractures of the upper third of the femoral shaft, the tilt used is 20 centimeters; this, however, could be increased or decreased by the use of additional small wooden blocks of the desired height under the two bedposts on the side of the traction or on the other side, respectively. All cases are roentgenologically controlled.

## USES

Figures 3 and 4 show the effect of bed tilting in maintaining abduction during traction treatment in 2 cases of fracture of the proximal third of the femoral shaft. These fractures are notorious for the abduction deformity of the proximal fragment, for which some surgeons used odd operative procedures such as the disinsertion of the pelvitrochanteric muscles.

Other instances in which this procedure can be used are fractures of the femoral neck, fractures of the acetabulum with central dislocation of the hip, and inflammatory conditions of the hip with adduction deformity.

## DISCUSSION

Several surgeons have used various methods to maintain abduction during traction of the lower limb (Fig. 2). Of these, the most famous is that of Anderson who, with a special apparatus, used the "well leg" to push the pelvis upward on the normal side, thus abducting the hip on the side under traction. The normal leg and thigh were fixed in plaster (Fig. 2c). Be-

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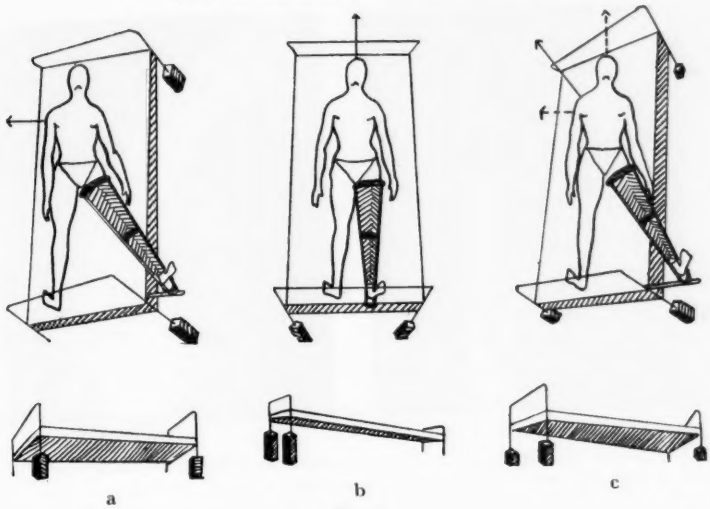



FIG. 1.

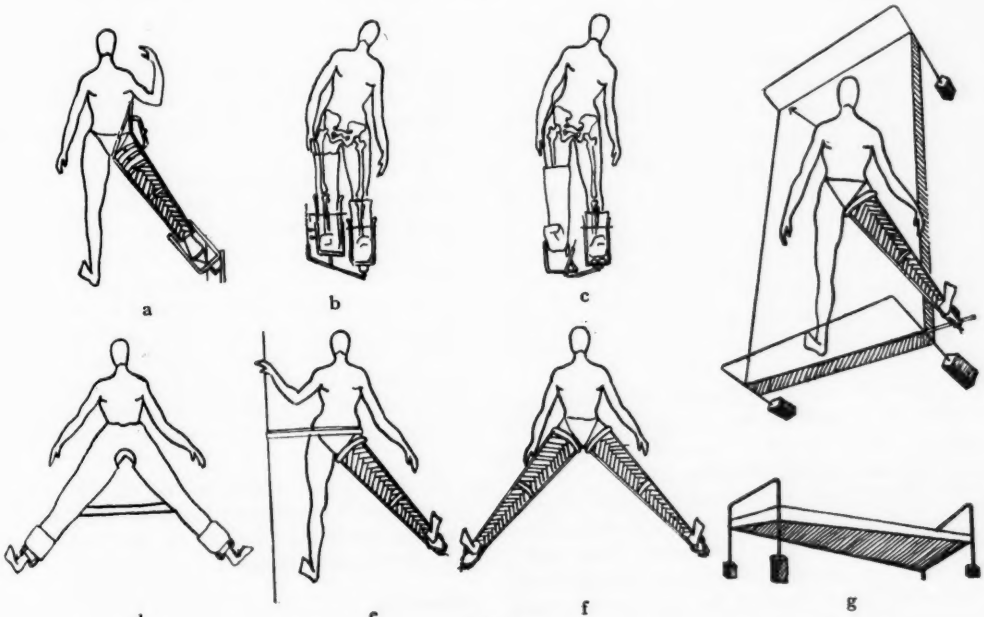
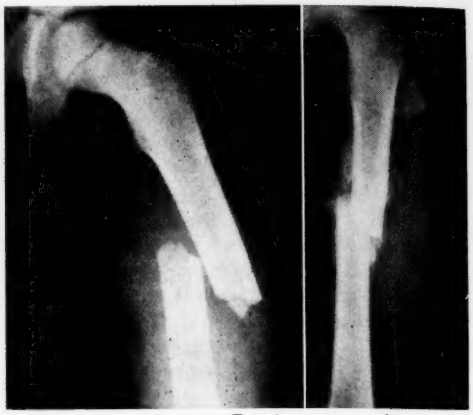



FIG. 2.

FIG. 1. Diagram demonstrating the effect on the patient's trunk of raising: a, the side of the bed alone; b, the foot of the bed alone; or c, the side and the foot of the bed together. The latter illustrates the method reported.

FIG. 2. Methods used by different surgeons to maintain abduction at the hip during traction: a, Huc; b, Steel and Grossman; c, Anderson; d, Thomson; e, Böhler; f, Desmarest, Planson, and Courtois-Suffit; g, the method herein described.

a Fig. 3. b



a Fig. 4. b

Fig. 3. Fracture of the proximal third of the femoral shaft with marked abduction of the proximal fragment, treated by skeletal traction and bed-tilting; a, before treatment, b, after treatment.

Fig. 4. Fracture of the femoral shaft at the junction of its proximal and middle thirds with abduction of the proximal fragment and overlap; a, before treatment, b, after treatment with skin traction and bed-tilting.

cause of the discomfort felt by the patient in the sole of the foot on the normal side and because of the danger of pressure necrosis of its skin, Steel and Grossman used "bone countertraction" with the splint, by inserting a Steinmann's pin in the tibia of the normal leg as illustrated in Figure 2b.

Huc used a modification of the Thomas splint in which the upper extremity of the lateral bar is extended upward at an obtuse angle to the side of the patient's trunk and is fixed to it by a plaster bandage, as may be seen in Figure 2a.

Desmarest, cited by Planson, and Courtois-Suffit used traction of the healthy as well as the affected leg, both put symmetrically in a position of forced abduction (Fig. 2f).

Thomson used plaster casts applied to both lower limbs that were maintained in full abduction by two wooden cross boards. Long moleskin traction straps were applied to both lower limbs, and the traction ropes were incorporated in the plaster (Fig. 2d).

Böhler strapped the pelvis to the side of the bed opposite to the traction (Fig. 2e).

Clavelin used a traction apparatus in which countertraction was maintained against the ischium of the normal side.

These methods have more than one of the following disadvantages: (1) fixation of the normal leg, with the danger of stiffness of its joints; (2) pressure on the sole of the normal foot; (3) discomfort; and (4) the need of a special apparatus.

In view of the disadvantages of the previous methods, the present technique has been developed. In it no special apparatus is used, and the normal limb is not fixed and does not therefore become stiff. The patient's trunk is free in bed. He is more comfortable, nursing is easier, and the patient can sit up. This position avoids chest and circulatory complications. Beside these advantages, the tilting of the bed is as good as any other method in maintaining abduction of the hip while under traction (Fig. 2g).

Such a simple technique can be very useful in the hands of country surgeons who, unlike the city specialist, have not all the modern implements at their disposal.

SUMMARY

The various methods used to abduct the hip while traction is applied to the lower limb were reviewed. A simple technique in which abduction is maintained by tilting the bed was described. This new method is useful, does not need any special apparatus, and with this procedure the patient's trunk, pelvis, and normal leg are left free.

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# SOME HAZARDS ASSOCIATED WITH MOBILIZATION OF THE LEFT LOBE OF THE LIVER

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DIVISION of the left triangular ligament with right lateral retraction of the left lobe of the liver is known as the Grey Turner maneuver. A number of years ago, Grey Turner of Newcastle said that he had first seen the procedure performed by the late Carl Eggers at Lenox Hill Hospital, New York.

Although this maneuver is simple to execute and of considerable aid in the exposure of the abdominal esophagus and the gastroesophageal junction, it is not without hazard. The object of this report is to point out the hazards associated with this procedure.

A 54 year old physician was found to have an extensive carcinoma of the upper esophagus. Preliminary abdominal exploration and mobilization of the stomach were carried out. Because of the extreme depth of the abdomen, some difficulty was encountered in mobilizing the cardia, and it was decided to divide the left triangular ligament and reflect the left lobe of the liver. The ligament was divided and the incision was carried beyond its division into the anterior and posterior layers of the coronary ligament. The final snip with the dissecting scissors entered the inferior vena cava. Because of the patient's habitus and the proximity of the diaphragm, control was extremely difficult to secure without compromising the lumen of the vessel (Fig. 1).

From the Department of Surgery, The Lahey Clinic, Boston.

The inferior vena cava and possibly the hepatic veins may be injured if the Grey Turner maneuver is carried too far to the right. The suggested procedure is to divide only the left triangular ligament; the incision should be stopped at the point where the left triangular ligament divides to form the layers of the coronary ligament.

Probably only the most innately meticulous surgeon would think of reattaching the left lobe of the liver after the dissection at the cardia has been completed. Yet this is a necessary step, as the following case reports demonstrate.

A transthoracic resection for a favorable lesion of the midesophagus was performed on an 82 year old patient. Preliminary mobilization of the stomach had been carried out, including section of the left triangular ligament. The patient responded well for 1 week, then began to vomit. After a few more days she could tolerate nothing by mouth. Barium series strongly suggested obstruction at the hiatus of the diaphragm. Since the stomach had been drawn into the thorax through the intact esophageal hiatus it was thought that perhaps narrowing had occurred at this level (Fig. 2). Laparotomy revealed that the mobilized left lobe of the liver had become reattached to the dia-

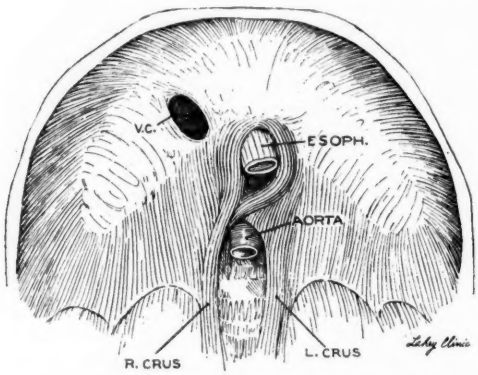


FIG. 1. The close relationship of the inferior vena cava to the hiatus as well as the abdominal esophagus is shown.

FIG. 2.

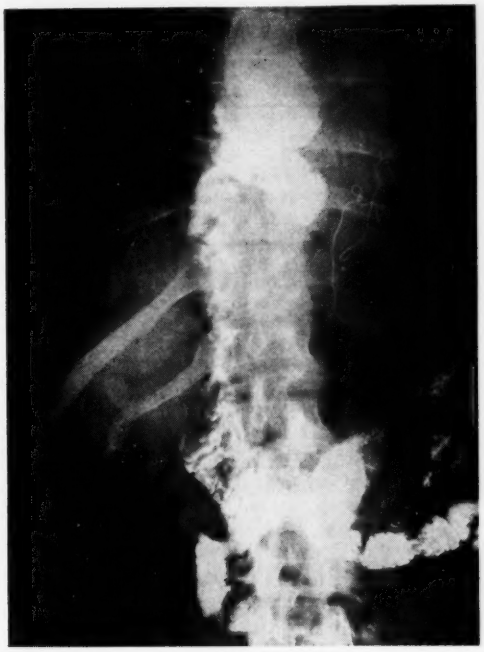

FIG. 3.

FIG. 2. Postoperative roentgenogram after ingestion of barium, showing complete gastric obstruction at the level of the hiatus.

FIG. 3. Roentgenogram shows incomplete obstruction of the antrum at the hiatus. This obstruction later became complete.

phragm in the region of the crus, thereby obstructing the antrum.

A second patient had a laparotomy preliminary to proposed right transthoracic resection of the esophagus. The Grey Turner maneuver was carried out and the esophageal hiatus was manually dilated. From early convalescence, the patient regurgitated all feedings. Eventually, obstruction of the stomach at the hiatus was demonstrated by roentgenogram (Fig. 3). Secondary laparotomy was necessary for relief, and findings completely similar to those in the previous case were revealed.

The mobilized left lobe of the liver tends to fall posteriorly and may become attached to the hiatal margin, causing obstruction of the transplanted stomach. It is suggested that the left triangular ligament be reattached to the under surface of the diaphragm with a few sutures and that care be taken to avoid the inferior phrenic vessels and the pericardium.

## SUMMARY

The Grey Turner maneuver is extremely useful in facilitating dissection of the abdominal esophagus, vagus nerves, and gastric cardia. Section of the left triangular ligament should be carried only to the beginning of the bare area to avoid injury to the inferior vena cava and hepatic veins. The left triangular ligament should be reattached to the diaphragm at the conclusion of the procedure.

# THE SURGEON'S LIBRARY

## *Reviews of New Books*

THE MONOGRAPH entitled *Management of the Aged Surgical Patient*[1] is devoted to the diagnosis and treatment of the surgical diseases most commonly a problem in the patient over 60 years of age. The experience of the author and his colleagues at the University of Iowa is drawn upon throughout the work and specific mortalities are summarized in the appendix. The excellent mortality figures, 6 per cent for those in the over 80 age group, are a tribute to the principles and practices outlined in this volume.

The increasing proportion of the aged in the population and the persistence of their many problems, essentially solved or nonexistent in younger people, make this a very important work. For example, the author points out that 20 years ago the mortality from appendicitis was highest in the teen-ager or young adult. Today, the mortality rate is highest in the aged. The death rate due to duodenal ulcer has increased markedly in the aged in recent years.

Emphasis is placed upon the decreased margin of error in the aged whether in diagnosis, operative technique, or in preoperative and postoperative care. While this volume is relatively small, the author has included many details of the management of patients not found in texts of greater length. Many useful illustrations of operative techniques can be found throughout the book.

This monograph is written in an easy, straightforward style and organized logically into a definition of the problem under consideration, preoperative preparation which includes a special section on the cardiac and diabetic patient, anesthesia, the operation and complications, acute conditions of the abdomen, arterial disease, trauma, urology, and miscellaneous problems of the aged.

The multiple factors that must be considered in order to achieve success in surgery in the aged are all well presented. One is impressed with the fact that most recommendations are based upon extensive personal experience.

Some might differ with the statements regarding the management of thrombophlebitis. The only other criticism which might be offered is the brevity in dealing with the aged patient undergoing thoracic surgery.

This concise monograph will be read with interest and profit by all surgeons and is recommended especially for surgical house officers.

—*Lloyd D. MacLean.*

MORE THAN 10,000 spines were removed at autopsy at the Dresden Institute of Pathology and studied anatomically and pathologically by Georg Schmorl and clinically and radiologically by Herbert Junghanns. The results of this investigation were combined in a monograph entitled *The Human Spine in Health and Disease*,[2] first published in 1932. This tremendous repository of information about the spine has been revised and amended through the years by Junghanns and appears now, for the first time, in English. The correlation between the anatomy or pathology and the roentgenogram is an outstanding feature of the book. The reproductions of the specimens and the roentgenograms are superb. A good deal of the excellence of the roentgenograms is due to the fact that the films were made from excised specimens with the consequent elimination of all overlying soft parts, gas shadows, and other artifacts. The book is complete and comprehensive without being bulky. The contents are simply organized and made easily available through an excellent index. The bibliography of nearly 3,000 references is up-to-date and includes all important works in the world literature.

—*Leonard D. Peltier.*

IN THE BOOK entitled *Chirurgie du rachis*,[3] André Sicard, Professor of the School of Medicine of Paris and Surgeon at the Beaujon Hospital, has reported upon the operative techniques of spinal surgery and the various problems encountered during the preoperative and postoperative periods. The author's experience is based upon approximately 3,000 personal cases.

The book is very comprehensive; the pathologic conditions are described as well as the treatment of traumatic, congenital, infectious, and neoplastic conditions of the spine. The author's good judgment regarding surgical intervention in these problems is

[1] MANAGEMENT OF THE AGED SURGICAL PATIENT. By Sidney E. Ziffren, M.D. 219 pages, 30 illustrations. $7.50. Chicago: The Year Book Publishers, Inc., 1960.

[2] THE HUMAN SPINE IN HEALTH AND DISEASE. ANATOMICOPATHOLOGIC STUDIES. By Georg Schmorl, M.D. Clinicoradiologic Aspects by Herbert Junghanns, M.D. First American Edition, translated and edited by Stefan P. Wilk, M.D., and Lowell S. Goin, M.D. 285 pages, 419 illustrations. $21.00. New York and London: Grune & Stratton, 1959.

[3] MONOGRAPHIES CHIRURGICALES (COLLECTION HENRI MONDOR). CHIRURGIE DU RACHIS. By André Sicard. 478 pages, illustrated. 7.000 fr. Paris: Masson et Cie, 1959.

demonstrated throughout the book. The two main principles are: (1) do not fuse a joint which roentgenologically appears to be normal; (2) do not fuse a pathologic joint which is not painful.

—*Marco Antonio Lazcano M.*

IN THE SECOND EDITION of *Heritable Disorders of Connective Tissue*[4] a wealth of material is presented regarding this subject. In no one previous volume has so much information been collected concerning hereditary conditions. The first chapter is on the clinical behavior of hereditary syndromes and this is followed by a chapter on the biology of normal connective tissue. Next, Marfan's syndrome is thoroughly discussed in a chapter which comprises nearly 100 pages. Ehlers-Danlos syndrome, osteogenesis imperfecta, Hurler's syndrome, and pseudoxanthoma elasticum are each discussed in separate chapters. A group of disorders classified by the author as more likely to be due to connective tissue disorders are discussed more briefly, followed by those conditions less likely to be caused by connective tissue disorders.

The list of references for each of the chapters is extensive, and the illustrations are numerous. The text is readable.

This is an extremely valuable book, and since the connective tissue disorders encroach upon every field of medicine it should be helpful in all specialties. This informative and interesting book concerns conditions about which the average internist, pathologist, orthopedic surgeon, or other specialist knows too little.

—*John H. Moe.*

A MASTERFUL PRESENTATION of the problems to be encountered and of sensible principles to be applied in caring for the overwhelming numbers of disaster casualties may be found in the book entitled *Surgical Philosophy in Mass Casualty Management*.[5] The authors are dedicated military surgeons who have had major surgical responsibilities in combat and who have taught combat surgical principles to a vast number of professional students.

In the chapter "Common Sense Recognition of the Problem," a blunt condemnation of the "naive, emotional, and academic statements" of inexperienced scientists outside of the fields of their competence lays a proper perspective for thoughtful study of problems to be faced and sound principles in management if the greatest good is to be accomplished with available medical personnel and supplies.

Succeeding chapters deal with characteristic effects of trauma, principles and importance of sorting, treatment groups, costs of delayed medical care, and chemical and bacteriologic warfare. Against this background, the authors draw many valuable lessons learned from civilian disasters and simulated casualty exercises performed in military and civilian institutions.

This volume defines responsibilities which must be met, compromises which are justifiable, and sound principles to be applied in hospital and community emergency plans. Our most important lessons have been learned from combat and civilian disasters. Wise counsel of combat surgeons should be heeded.

—*Sam F. Seeley.*

THE AUTHOR of the first pediatric surgical monograph *Intussusception in Infants and Children*[6] has set a high standard of excellence for this series. The sections covering the historical, pathologic, and experimental aspects of intussusception are enjoyably written, well documented, beautifully illustrated, and particularly enlightening to a student of this subject. Diagnosis and difficulties in diagnosis are dealt with in a fashion which will interest all concerned with the day-to-day care of infants and children. The sections on treatment are well documented with detailed analysis of the existing literature and, as presented, make a strong case for the author's belief that: (1) qualified surgeons should be responsible for the treatment of all cases of intussusception; (2) hydrostatic barium enema reduction can be safely used on all infants and children who suffer from intussusception if the usual general supportive measures are instituted prior to the initiation of the reduction; (3) an operating room and team be ready to complete the reduction in all cases in which nonsurgical efforts failed.

The author's own program for management is clearly outlined and includes careful attention to the specific details of having not more than 3½ feet of hydrostatic pressure, avoiding manipulation of the abdomen, insisting on a clear-cut demonstration of complete reduction of the intussusception by evidence of a generous reflux of barium into the terminal ileum, disappearance of the abdominal mass, abatement of all symptoms, and finally, the passage of charcoal instilled into the stomach via the rectum. Failure to complete the reduction which occasionally requires 45 to 60 minutes is followed by immediate laparotomy, usually through a McBurney incision on the right side. The advantages of the combined approach to the reduction of intussusception include reduction in morbidity; avoidance of unnecessary operation and postoperative complications, particularly adhesions; and in cases of incomplete reduction the previous barium reduction makes the intra-abdominal surgery less extensive. In no instance did perforation of the bowel or reduction of the nonviable intestine occur in the author's series. Pre-existing associated lesions, usually a Meckel's diverticulum, were, in general, irreducible.

This book is an important addition and a particularly useful summation of existing information dealing with a controversial subject.

—*H. William Clatworthy, Jr.*

FOR THE FIRST TIME in the history of anesthesia, a definitive text on the subject has been made available to both student and teacher. Broad in its parameters of discussion, yet specific in its approach to those

[4] HERITABLE DISORDERS OF CONNECTIVE TISSUE. Victor A. McKusick, M.D. 2nd ed. 333 pages, illustrated. $12.00. St. Louis: The C. V. Mosby Co., 1960.

[5] SURGICAL PHILOSOPHY IN MASS CASUALTY MANAGEMENT; WITH DETAILED NOTES ON PRACTICAL CARE. By Warner F. Bowers, A.B., B.Sc., M.D., M.S., Ph.D., and Carl W. Hughes, A.B., M.D. 204 pages. $6.75. Springfield, Ill.: Charles C Thomas, 1960.

[6] INTUSSUSCEPTION IN INFANTS AND CHILDREN. By Mark M. Ravitch, M.D. 121 pages, illustrated. $9.00. Springfield, Ill.: Charles C Thomas, 1959.

matters which require specificity, *A Practice of Anaesthesia*[7] provides both the practitioner and academician with a reference text that can stand the test of time.

The foreword by M. D. Nosworthy defines very well the qualifications of the authors as "recognized teachers and acknowledged authorities in anaesthesia," and outlines the novel concept in presentation as he says, "contrary to usual anaesthetic custom, the subject has been arranged in sections devoted to the various systems of the body. Frequent repetition—so difficult to avoid in a work of such magnitude—has been obviated by cross-reference, and the comprehensive index is there to be used."

Since these British authors write of, and about, equipment with which they are intimately familiar, the American reader may be confused by the descriptions and explanations of this facet of anesthesia. Obviously, the references are predominantly from the British literature, and this the American reader may also find discomfiting. These, however, are deficits in the reader rather than in the authors.

It is doubtful that any other text on this subject in the next 20 years will be received as enthusiastically as has been this one. —*J. Gerard Converse.*

THE AUTHOR of the volume *Essentials of Orthopaedics*[8] has again produced another outstanding textbook for the medical profession. He has augmented the second edition with more material without increasing the size of the book. This gives the reader the benefit of clarity which testifies to the author's vast experience and wisdom. He has properly weighted his efforts on the more important and the more common conditions seen. Particularly helpful are the diagrams so essential to elucidate the more complex concepts. The author suggests preferred treatment in orthopedics. To the delight of the reader, he abstains from the historical treatment for the sake of completeness. The author considers fractures a separate subject and they have not, therefore, been included. The book is a classical text for medical students and a quick reference source for all physicians interested in the field of orthopedics.

—*Harley M. Sigmond.*

A TEXTBOOK written with a specific aim and purpose should be judged on how well it has, or has not, accomplished the desired end. The authors of the *Textbook of Otolaryngology*[9] state that it was designed for the medical student and for the general practitioner.

Medical knowledge is advancing so rapidly that any textbook attempting to encompass all of the medical or surgical lore in any field is, of necessity, of considerable length and complexity. Such a book, thus, loses much of its worth as a textbook for students. It is becoming increasingly important that the author of any book aimed at those of the student level cull the vast amount of available knowledge, ruthlessly discarding that material which is no longer pertinent and that which is too detailed or too complex, in order to present a text that is concise but still accurate. Such a book will enable the student to acquire a matrix of learning to which he may then add the detailed knowledge available to him in the more encyclopedic works and in the current literature. The authors of this work have had the problem of editing for the student as their primary goal, and have accomplished their aim in an admirable manner.

The first section deals with the technique of the physical examination of the areas with which the otolaryngologist is involved. The remainder of the book is devoted to the anatomy, physiology, and the pathology of each of the several subdivisions of the areas involved in the sphere of otolaryngology. These are presented in the sequence that most otolaryngologists follow in conducting a detailed physical examination of the structures in the head, neck, and tracheobronchial tree.

The discussions of the anatomy and physiology are simple, short, accurate, and entirely adequate for this type of textbook. The descriptions of the diseases of the areas and their treatment are also minimal, but cover most, if not all, of the pathologic conditions most commonly encountered.

The material presented in each of the chapters is very clearly written and illustrated. Perhaps the one chapter that epitomizes the form and character of the entire textbook is that written on the physiology of hearing. This description is accomplished in 10 pages of text and illustrations and is a perfect example of how well the authors have accomplished the task which they set for themselves.

The size and the clarity of the photographs are outstanding and are extremely well selected to illustrate the points under consideration. The diagrams and drawings are equally well chosen and large sized.

The authors have produced a practical textbook that will be most helpful to those involved in teaching otolaryngology to the medical student; it deserves to be recommended, if not required, reading for this group. —*Fletcher Austin.*

AT FIRST GLANCE it seems unlikely that the book entitled *Treatment of Urinary Lithiasis*[10] could contain enough material to justify its 512 pages. However, as the titles of the 29 chapters demonstrate, the problem of stone formation and its control encompasses many different fields of medicine and its allied sciences. Such diverse considerations as the surgical treatment of calculi in different portions of the urinary tract, the recognition and treatment of hyperparathyroidism, and the role of colloid science in the treatment of urinary lithiasis seem to be unquestionably within the scope of the topic selected for discussion. The coverage of most phases of the treatment of urinary lithiasis is exhaustive. For the most part, the 32 authors contributing to the book have maintained an easily read-

[7] A PRACTICE OF ANAESTHESIA. By W. D. Wylie, M.A., M.B.(Cantab.), M.R.C.P., F.F.A.R.C.S., and H. C. Churchill-Davidson, M.A., M.D.(Cantab.), F.F.A.R.C.S. 1056 pages, 246 illustrations. $20.00. Chicago: The Year Book Publishers, Inc., 1960.

[8] ESSENTIALS OF ORTHOPAEDICS. By Philip Wiles, M.S.(Lond.), F.R.C.S.(Eng.), F.A.C.S. 3rd ed. 576 pages, 417 illustrations. $13.00. Boston: Little, Brown & Co., 1959.

[9] TEXTBOOK OF OTOLARYNGOLOGY. By David D. DeWeese, M.D., and William H. Saunders, M.D. 464 pages, 354 illustrations. $8.75. St. Louis: The C. V. Mosby Co., 1960.

[10] TREATMENT OF URINARY LITHIASIS. Compiled and edited by Arthur J. Butt, B.S., M.D., F.A.C.S. 577 pages, illustrated. $21.00. Springfield, Ill.: Charles C Thomas, 1960.

able style which is complimented by excellent printing and reproductions. As might be expected in a subject as complex and indefinite as this, the authors often find it necessary to rely heavily on personal experience and opinion; differences in these have led to occasional disagreements and contradictory statements. Although the overlapping coverage of subjects tends to increase the opportunity for this expression of differences, it seems necessary to maintain the value of the monograph as a reference source. Detailed consideration is given to the attempts to control calculous formation by medical means; chapters are devoted to the management of patients with nephrocalcinosis, recumbency calculi, cystine lithiasis, uric acid nephropathy, and to patients with calculi associated with an abnormal excretion of calcium and phosphorus. In addition, a discussion of the Shorr regimen for patients with phosphatic calculi is presented.

A complete author and subject index adds to the value of the book as a reference source. The extensive bibliography included by many of the authors also contributes to its worth. Most of the important concepts currently employed in the treatment of urinary lithiasis are clearly presented in this monograph. The range of subjects covered should give it rather widespread appeal among the medical profession in general and urologists in particular.

—*John T. Grayhack.*

THE VOLUME on *Primary Tumors of the Calvaria*[11] is concise, readable, and well illustrated. Since most of the literature on this subject can be found only by an assiduous search of periodicals and roentgenologic and pathologic textbooks, there is a need for such a monograph.

The material is divided into benign tumors of the calvaria such as osteoma, hemangioma, giant cell tumor, chondroma, and lipoma; tumor-like lesions of the calvaria due to xanthomatosis and fibrous dysplasia; and malignant tumors of the calvaria including osteogenic sarcoma, fibrosarcoma, myeloma, and malignant hemangioendotheliomas. The author does not include metastatic tumors of the calvaria or cases in which the skull is involved with meningioma. Tumors of the base of the skull, such as ethmoid groove osteomas or epidermoid sinus tracts extending to intracranial epidermoid cysts, are omitted.

Although this book contains only 105 pages, brevity has not been obtained at the expense of clarity or detail. A bibliography is included at the end of each chapter for those who seek a more detailed account of some aspects of the calvaria tumors described.

—*Vernon H. Mark.*

THE AUTHOR of the monograph *Back Pain*[12] is a special lecturer in the Department of Physical Medicine at the Medical School, College of Medical Evangelists, Los Angeles.

His method is described as being especially suitable for the relief of symptoms which might arise in any part of the spine and are not caused by herniated disks or other gross pathologic processes.

Osteoarthritis, trauma, and infectious, suppurative, and rheumatoid arthritis are described as pathologic conditions. Traumatic synovitis and traumatic hemarthrosis occur. He recognizes tears and rupture of ligaments as well as muscle injuries, such as simple contusions, fibromyositis, and scar tissue following inflammation. Muscle spasm and muscle atrophy are secondary to primary joint dysfunction. The author points out that roentgenograms show only well advanced pathologic changes and that negative x-ray and normal laboratory findings do not rule out the true causes of back pain.

Trauma is defined as abnormal force which produces some mechanical derangement in the joint or joints. Pathology is defined as anything which is not physiologic. The word disease is limited to pathologic conditions not related to trauma. He states that all pathologic conditions of the back cause limitation of movement of the affected part of the spine.

The technique for the examination of low back, thoracic spine, and cervical spine is described. Therapeutic manipulation is discussed and for the most part the methods are the same as for the diagnostic techniques given for examination of the back.

In addition to the manipulative method, heat, massage, rest, and back support are advised. The importance of good posture is emphasized.

Conditions which complicate dysfunction of the back are described. There is a chapter on prolapsed intervertebral disks and one on whiplash injuries of the cervical spine.

—*Emil D. W. Hauser.*

VOLUME I of a proposed series of three atlas presentations of anatomy and surgical approaches has been developed at the State University of Iowa, Orthopedic Department. The *Atlas of Anatomy and Surgical Approaches in Orthopaedic Surgery*[13] reflects the development of an anatomic-surgical museum and is a notable contribution to the current literature.

The dissections are obviously meticulous and skillful, and the photography has been done in an unusually successful manner. The text is lean but adequate, and continuity is provided by photographs of surface relationships of incisions.

While there may be discussion on the relative merits of photographs and artists' drawings to depict anatomic structures, one point stands in favor of the photographs, that is, the subject of anatomy is originally approached from dissections of prepared specimens and the process of review and study may best be reinforced by books which stimulate this technique and assist in imagery and recall.

This volume has been supported in part by the Orthopaedic Research and Education Foundation, and it is hoped that support will continue for the prompt preparation of the additional volumes on the lower extremities and the trunk.

—*J. William Hillman.*

[11] PRIMARY TUMORS OF THE CALVARIA; WITH SPECIAL CONSIDERATION OF THE CLINICAL PROBLEMS. By Franklin Jelsma, M.D. 116 pages, illustrated. $7.00. Springfield, Ill.: Charles C Thomas, 1960.

[12] BACK PAIN; DIAGNOSIS AND TREATMENT USING MANIPULATIVE TECHNIQUES. By John McM. Mennell, M.D. 226 pages, 78 illustrations. Boston and Toronto: Little, Brown & Co., 1960.

[13] ATLAS OF ANATOMY AND SURGICAL APPROACHES IN ORTHOPAEDIC SURGERY; UPPER EXTREMITY. By Rodolfo Cosentino, M.D. With a preface by Arthur Steindler. 192 pages, 134 illustrations. $10.50. Springfield, Ill.: Charles C Thomas, 1960.

## BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selection will be made for review in the interests of our readers and as space permits.

Tumors of the Female Sex Organs. Part 2. By Arthur T. Hertig, M.D., and Hazel Gore, M.B., B.S. 275 pages, illustrated. $2.50. Washington: Armed Forces Institute of Pathology, 1960.

Recent Advances in Biological Psychiatry. Edited by Joseph Wortis, M.D. Vol. II. 417 pages, illustrated. $13.50. New York: Grune & Stratton, Inc., 1960.

The History of the Royal College of Surgeons of England. By Zachary Cope, Kt. 360 pages, illustrated. $13.50. Springfield, Ill.: Charles C Thomas, 1960.

Tumors of Childhood. By Harold W. Dargeon, M.D. 476 pages, 315 illustrations. $20.00. New York: Paul B. Hoeber, Inc., 1960.

Trauma in the Aged. Edited by Edgar M. Bick, M.D. 524 pages, illustrated. $16.00. New York: McGraw-Hill Book Co., Inc., 1960.

A Short History of Obstetrics and Gynecology. By Theodore Cianfrani, M.D. 449 pages, illustrated. $12.50. Springfield, Ill.: Charles C Thomas, 1960.

Fluid Balance in Obstetrics; a Critical Review. By Philip Rhodes, M.B., F.R.C.S.(Eng.). 169 pages. $5.75. Chicago: The Year Book Publishers, Inc., 1960.

Current Surgical Management II. A Book of Alternative Viewpoints on Controversial Surgical Problems. Edited by John H. Mulholland, M.D., Edwin H. Ellison, M.D., and Stanley R. Friesen, M.D., with contributions by 50 authorities. 348 pages, illustrated. $8.00. Philadelphia and London: W. B. Saunders Co., 1960.

Biomechanics of the Central Nervous System; Some Basic Normal and Pathologic Phenomena. By Alf Breig. 183 pages, illustrated. $8.50. Chicago: The Year Book Publishers, Inc., 1960.

Neoplasms of Bone and Related Conditions; Etiology, Pathogenesis, Diagnosis, and Treatment. 2nd ed. By Bradley L. Coley, M.D. 862 pages, illustrated. $30.00. New York: Paul B. Hoeber, Inc., 1960.

A Catalogue of the Portraits and Other Paintings, Drawings, and Sculpture in the Royal College of Surgeons of England. By William LeFanue. 120 pages, illustrated. $6.75. Edinburgh and London: E. & S. Livingstone Ltd., 1960; Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

La fertilité cyclique de la femme; méthode facile de régler les naissances par la mesure de la temperature basale. By J. G. H. Holt. 3rd ed. 80 pages, illustrated. Paris: Vigot Freres, Editeurs, 1959.

Obstétrique. By Martial Dumont. 660 pages, illustrated. Paris: Vigot Freres, Editeurs, 1960.

I tumori retroperitoneali. By G. F. Pellegrini and G. Caraffa, with the collaboration of C. Crosta. 306 pages, illustrated. Milan: Edizioni Minerva Medica, 1960.

Collected Papers of the Mayo Clinic and the Mayo Foundation. Compiled by George G. Stilwell, M.D. Vol. 51—1959. 828 pages, illustrated. $14.00. Philadelphia and London: W. B. Saunders Co., 1960.

Symposium on Salt and Water Metabolism. New York Heart Association. New York City, December 11–12, 1959. Edited by Alfred P. Fishman, M.D. $2.00. Supplement of *Circulation:* Vol. XXI, No. 5, Part 2, May 1960. New York: American Heart Association, 1960.

Intra-osseous Venography. By Robert A. Schobinger, M.D. 245 pages, 317 illustrations. $14.50. New York and London: Grune & Stratton, 1960.

Hormontherapie in der Frauenheilkunde. 2nd ed. By Dr. Joachim Ufer. 165 pages, illustrated. $8.00. Berlin: Walter de Gruyter & Co., 1960.

Zwangerschap, Gynaecologie en Schildklier. By Jacob Johannes Bol. 124 pages, illustrated. Groningen: Drukkerij I. Oppenheim N.V., 1960.

# *Correspondence*

## AN EVALUATION OF THE ONE STAGE, LOW ANTERIOR RESECTION—*A Correction.*

In the article entitled "An Evaluation of the One Stage, Low Anterior Resection" by Charles W. Mayo and P. Kent Cullen, Jr. which appeared in the July 1960 issue of the Journal on page 82, an editorial deletion made it appear that 362 one stage, low anterior resections were performed at the Mayo Clinic from January 1935 through December 1958. The fact is that this number of resections was performed by Charles W. Mayo alone during this period of time.

# AMERICAN COLLEGE OF SURGEONS

OWEN H. WANGENSTEEN, Minneapolis, *President*
I. S. RAVDIN, Philadelphia, *President-Elect*

## *PRELIMINARY PLANS FOR THE 46th CLINICAL CONGRESS CIVIC AUDITORIUM, SAN FRANCISCO, CALIFORNIA 10 TO 14 OCTOBER 1960*

THE DAILY SCHEDULE of the Forum on Fundamental Surgical Problems appears in detail in this issue as well as an outline of the motion picture and television programs. The preceding three issues of SURGERY, GYNECOLOGY & OBSTETRICS have outlined other portions of the Clinical Congress program. One of the most stimulating events at the Clinical Congress each year is this presentation of surgical research-in-progress in the nation's medical schools and other medical institutions. These developments in surgery will be presented Monday through Thursday, morning and afternoon, by young surgeons and research scientists from all parts of this country and Canada.

For Fellows whose dues are paid to 31 December 1959 there is no registration fee; those whose dues are not paid as of this date pay $40.00. Non-Fellows pay $40.00. Members of the Federal Services pay $20.00. No fee is required of Initiates, members of the Candidate Group, and surgical residents. Everyone attending a Postgraduate Course pays a fee of $5.00. To expedite registration, it is requested that everyone carry medical identification. Official registration forms are now available from College headquarters. If you plan to come, please write immediately for these forms: American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois.

While the primary purpose of the Clinical Congress is instructive, San Francisco offers many points of interest for leisure hours. In addition, the San Francisco Opera Company, co-operating with the American College of Surgeons, has set aside 1,000 seats for Bellini's opera "La Sonnambula" and a performance by the San Francisco Ballet Company on Thursday, 13 October. The Ladies' Entertainment Committee, under the chairmanship of Mrs. Leon Goldman and Mrs. Edwin J. Wylie, has prepared a week's program of interest and fun for doctors' wives.

## *Forum on Fundamental Surgical Problems*

**Monday, 8:30 a.m.—12:00 noon**

TISSUE TRANSPLANTATION

Studies on Orthotopic Homotransplantation of the Canine Heart. RICHARD R. LOWER and NORMAN E. SHUMWAY, Palo Alto.

Autotransplantation of Liver Tissue. BJORN THORBJARNARSON, CHARLES MCSHERRY, EDWARD RING, CHARLES FREY, and JOHN M. BEAL, New York.

Storage of Parathyroid Tissue in the Frozen State. PAUL S. RUSSELL, R. F. GITTES, and E. M. SPARROW, Boston.

Study of the Homograft Reaction by Retransplantation of the Canine Kidney. OKAS BALANKURA, WILLARD E. GOODWIN, JOSEPH E. MURRAY, and GUSTAVE J. DAMMIN, Boston.

Successful Renal Autografts in the Dog After 7 Hour Selective Kidney Refrigeration. JOSEPH C. KISER, HARRISON H. FARLAY, GILBERT F. MUELLER, CLAIRE J. STROBEL, and CLAUDE R. HITCHCOCK, Minneapolis.

Mass Homotransplantation of Abdominal Organs in Dogs. T. E. STARZL and HARRY A. KAUPP, Chicago.

A Comparison of Whole Spleen Autografts, Shielded Spleen, and Whole Spleen Homogenates in the Treatment of Irradiation Sickness in Dogs. RICHARD LILLEHEI, J. LONGERBEAM, E. YUNIS, and S. HILAL, Minneapolis.

DNA Synthesis in Regional Lymph Nodes During Skin Homograft Rejection. J. PIERCE, W. MEEKER, D. WEINER, R. WEINER, and RICHARD L. VARCO, Minneapolis.

The Resistance of Bone Marrow to Direct Irradiation. R. L. WEBB, S. W. JACOB, J. H. STONE, and J. ENGLEBERT DUNPHY, Portland.

The Influence of Sulfasuxidine upon the Response of Canine Small Intestine to Irradiation (4,000 r). JOHN S. SPRATT, JR., and PETER HEINBECKER, St. Louis.

Teflon As a Tendon Substitute. ROGER D. WILLIAMS, Columbus, Ohio.

Circumferential Replacement of the Trachea with Marlex Mesh. ARTHUR C. BEALL, JR., O. BREWSTER HARRINGTON, FRANCIS C. USHER, and GEORGE C. MORRIS, JR., Houston.

**Monday, 8:30 a.m.—12:00 noon**

GENERAL PROBLEMS

Alteration of the Effects of Jejunocolic Fistula; an Experimental Study. EDWARD W. JEW, JR., BERNARD S. LEVOWITZ, DONALD E. GWILLIM, and BERNARD FISHER, Pittsburgh.

The Production of Ulcerative Colitis by Anticolon Sera. HARRY H. LEVEEN, WILLIAM S. CALEM, and GERALD FALK, Brooklyn.

The Use of Fibrinolysis in the Prophylaxis of Peritoneal Adhesions. PASCHAL M. SPAGNA and GERALD W. PESKIN, Philadelphia.

Hemodynamic Studies in Transfusion Reactions. WILLIAM DEMARIA, DONALD SILVER, and WILLIAM G. ANLYAN, Durham.

Tolerance of Acute Hypovolemia During Cyclopropane and Fluothane Anesthesia. DOYLE P. SMITH, LEONARD W. FABIAN, and MARION A. CARNES, Jackson.

Comparison of Right-Left Ratios of Dried Lung Weight and Pulmonary Function. DELMAR CALDWELL, M. T. LATEGOLA, and JOHN A. SCHILLING, Oklahoma City.

The Use of Human Fibrinolysin by Aerosol in the Treatment of the Pulmonary Hyaline Membrane; Studies on the Fibrinolytic System of Normal Premature Babies and Older Children. J. LEONEL VILLAVICENCIO, EDUARDO JURADO, JOSEFINA SAGAON, and J. ALVAREZ DE LOS COBOS, Boston.

The Effect of Generalized Hypothermia on Ammonia Metabolism. ALFRED M. KEIRLE, ROBERT W. BUBEN, JOHN J. MCGLOIN, SANFORD L. WRIGHT III, and WILLIAM A. ALTEMEIER, Cincinnati.

The Effect of Thiotepa upon the Liver Utilizing a New Isolation-Perfusion Technique. JOHN E. HEALEY, JR., J. LESLIE SMITH, JR., R. LEE CLARK, JR., JOHN S. STEHLIN, JR., and E. C. WHITE, Houston.

Experimental Production of Hepatocellular Damage with Cortisone. M. C. ANDERSON, J. J. BERGAN, and J. SALEN, Chicago.

An Ion-Exchange Resin Artificial Kidney. HERBERT E. COHN, ARTHUR J. WEISS, JAMES E. CLARK, and THOMAS F. NEALON, JR., Philadelphia.

The Electronic Production of Co-ordinated Limb Movements. ADRIAN KANTROWITZ and RENE KHAFIF, Brooklyn.

**Monday, 8:30 a.m.—12:00 noon**

TUMORS

The Experimental Superiority of A8103 (Piperazine Derivative) over Other Agents in Prevention of Tumor Growth. ALAN DAVIES and FREDERIC A. DEPEYSTER, Chicago.

Protection Against Systemic Toxicity Due to Nitrogen Mustard. CHARLES A. ROSS, DAVID M. CARBERRY, and GUNTHER E. KRAUS, Buffalo.

The Role of the Spleen in Prevention of Nitrogen Mustard Toxicity. ANTONIO DEMETZ, FREDERIC P. HERTER, and SUSAN EVANS, New York.

Effects of Colchicine and Nitrogen Mustard on Ehrlich's Ascitic Tumor in Mice. ROBERT F. RYAN, HOMER L. LOCKRIDGE, and DELMAS A. JACKSON, New Orleans.

Nitrogen Mustard Perfusion of the Isolated Lung. C. F. BAXTER, J. T. GOSWITZ, and KARL P. KLASSEN, Columbus, Ohio.

Cancer Chemotherapy Using Antimetabolite-Metabolite Combinations. FREDERIC P. HERTER, ALFRED MARKOWITZ, JOHN B. PRICE, SANFORD G. WEISSMAN, and ANTONIO DEMETZ, New York.

Factors Concerned with the Metastatic Potential of Circulating Cancer Cells. OLGA JONASSON, Chicago.

The Role of Hepatic Damage on Tumor Development of the Walker 256 Carcinosarcoma. PAUL CHAN, GERALD O. MCDONALD, and WARREN H. COLE, Chicago.

Effect of Reticuloendothelial Interference on Experimental Metastases. EDWIN R. FISHER and BERNARD FISHER, Pittsburgh.

A Study of the Factors Concerned with Metastatic Spread of the Walker 256 Tumor in Rats' Hind Limbs. G. J. FRANCIS, B. J. GREENHILL, and CECIL M. COUVES, Edmonton.

Further Studies of the Effect of Local Sublethal Tumor Irradiation on the Development of Distant Metastases. PETER D. OLCH, J. K. STEVENSON, and HENRY N. HARKINS, Seattle.

The Time of Metastatic Spread. JOSEPH G. FORTNER, SARAB S. BHATIA, and PHYLLIS A. GEORGE, New York.

**Monday, 1:30—5:00 p.m.**

TUMORS

Viruses and Cancer; Experimental Studies of Human Malignant Disease. JAMES T. GRACE, JR., S. J. MILLIAN, E. A. MIRAND, and R. S. METZGAR, Buffalo.

Induction of Acute Hemolytic Anemia and Tumor-Like Lesions by an Infectious Cancer-Immunizing Agent of Rats. JEROME H. SACKS, RICHARD F. CLARK, and RICHARD H. EGDAHL, Richmond.

Serotonin for Conditioning of the Animal Host. NADIA CONVALIUS, Philadelphia.

Inhibition of Carcinogen Induced Mammary Cancer in Rats With Corticosteroid. L. F. MOCK, W. BAKER, R. COLLINS, and JOHN V. PROHASKA, Chicago.

The Hypercalcemia of Metastatic Breast Cancer. ARTHUR N. THOMAS, HANS F. LOKEN, GILBERT S. GORDON, and LEON GOLDMAN, San Francisco.

The Effect of Smoke and Non-Smoke Gases on Cells in Cell and Organ Cultures. PHILIP COOPER and IRENE P. GOLDRING, New York.

The Experimental Creation of an Internal Biliary Fistula to Facilitate Estrogen Excretion. PETER HAIRSTON, E. MEREDITH ALRICH, and VINCENT P. HOLLANDER, Charlottesville.

The Influence of Clorpactin XCB on the Spread of Tumors of the Colon. M. ATIK, FRANKLIN MASSARI, and ISIDORE COHN, JR., New Orleans.

The Value of Cytologic Studies During Proctosigmoidoscopy Examination for the Detection of Carcinoma of the Colon. ALAN B. CAMERON and HARVEY E. KNOERNSCHILD, Columbus, Ohio.

Tetracycline in Tumor. JOHN F. MCLEAY, BENEDIT R. WALSKE, and RICHARD E. OGBORN, Omaha.

Effect of DNA on Tumor Growth and Resistance to Chemotherapy. DONALD J. FERGUSON, Minneapolis.

A Method of Investigating the Metabolism of Tumors and the Influence upon Them of Antimetabolites. D. A. BOYES, R. E. BECK, F. R. C. JOHNSTONE, and C. R. MUIRHEAD, Vancouver.

**Monday, 1:30—5:00 p.m.**

HYPOTHERMIA

A Study of the Effects of Complete Circulatory Arrest on the Profoundly Hypothermic Dog. ALAN M. LESAGE, JOHN FREESE, W. GLENN YOUNG, JR., and WILL C. SEALY, Durham.

A Study of Oxygen Consumption During Profound Hypothermia Induced by Perfusion of the Entire Body. SHINOBU KAMEYA, MUSTAFA OZ, WILLIAM E. NEVILLE, and GEORGE H. A. CLOWES, JR., Cleveland.

The Physiological Effects of Deep Hypothermia for Intracardiac Surgery Without an Oxygenator. ARCHER S. GORDON, BERTRAND W. MEYER, and JOHN C. JONES, Los Angeles.

Observations on the Temperatures in the Brain During Extracorporeal Differential Hypothermia. W. ZINGG and S. KANTOR, Winnipeg.

An Experimental Study; an Apparatus for Regional Kidney Hypothermia. ABRAHAM T. COCKETT, Los Angeles.

Objective Evaluation of Myocardial Blood Supply in Vivo Through Observation of Acute Changes in Myocardial Temperature. EDWARD I. GOLDSMITH, New York.

Further Studies on Myocardial Metabolism During Elective Cardiac Arrest and Hypothermia. R. G. ELLISON, S. A. SINGAL, W. H. MORETZ, E. L. BRACKNEY, W. F. BUTLER, W. C. MALOY, J. H. ROSSI, and D. P. HALL, Augusta.

An Experimental Approach to the Supercooling of Canine Hearts. S. W. JACOB and R. L. WEBB, Portland.

Electrocardiographic Alterations Induced by Incisions in the Distal Conduction System. LAURENCE M. RIVKIN and HERMAN N. UHLEY, San Francisco.

Changes in Cardiac Conduction Produced by Ischemia and Hypoxia. ALBIN A. BAGDONAS, JACKSON H. STUCKEY, BRIAN F. HOFFMAN, JUAN PIERA, PAUL F. CRANEFIELD, and NORMAN S. AMER, Brooklyn.

The Arterial Supply of the Interventricular Septum and Atrioventricular Conduction. JUAN PIERA, JACKSON H. STUCKEY, ALBIN A. BAGDONAS, and CLARENCE DENNIS, Brooklyn.

Experimental Pulmonary Arteriovenous Fistula. MARTIN L. DALTON, JR., and JAMES D. HARDY, Jackson.

**Monday, 1:30—5:00 p.m.**

ORTHOPEDIC SURGERY

The Fate of Surgically Created Osteochondrial Fractures in Adult and Young Dogs. ROBERT W. BAILEY and DANIEL E. HABEL, Ann Arbor.

Experimentally Produced Legg-Perthe-Like Changes in Rabbits. R. K. GREENLAW, D. S. KAHN, and J. G. PETRIE, Montreal.

A Method for Obtaining Ionic Gradients Across Living Bone. MELVIN POST and J. O. GALANTI, Chicago.

The Vasodilatory Response to Skeletal Trauma. JAMES B. WRAY and MERRILL P. SPENCER, Winston-Salem.

Fat Embolism in the Rat. K. S. MORTON and M. J. KENDALL, Vancouver.

Studies on the Pathogenesis of Collagen Tissue Changes in Alcaptonuria. ROBERT AUSTIN MILCH, Baltimore.

Energy Expenditure During Early and Late Convalescence from Multiple Fractures. HARVEY A. ZAREM, JOHN M. KINNEY, and SHEILA NICHOLS, Boston.

Experiments on Pyogenic Arthritis. BERNIE P. DAVIS and JOHN RING, Buffalo.

The Treatment of Penicillin Resistant Staphylococcus Aureus Joint Infections with Intra-articular Broad Spectrum Antibiotics. CHARLES J. FRANKEL, CURTIS V. SPEAR, ROBIN HICKS, and T. HSU, Charlottesville.

Polyurethane Foam (Ostamer); Its Use in Experimental Animals and Investigation of Tissue Reactions. R. K. MACOOMB, C. HOLLENBERG, and W. ZINGG, Winnipeg.

Scoliosis; the Effect of Unilateral Resection of the Paraspinal Musculature in Normal and Bipedal Rats. JAMES W. DINSMORE and LYNN O. LITTON, Kansas City, Kansas.

Perimetric Analysis of Scoliosis; a Three Dimensional Concept. J. WILLIAM HILLMAN, Nashville.

**Tuesday, 8:30 a.m.—12:00 noon**

FLUIDS AND METABOLISM

Insensible Water Loss of Patients Undergoing Laparotomy. JOHN S. BRADSHAW and W. E. ABBOTT, Cleveland.

Chloride, Sodium, and Water Absorption in the Dog Jejunum, Ileum, and Colon. ERNEST M. BERKAS and EUGENE GRIM, Minneapolis.

The Role of the Spleen and Small Bowel in Uric Acid Production. JACK M. ZIMMERMAN, BERTON C. PRESSMAN, DAVID V. COHN, MARIE H. CARR, and PAUL R. SCHLOERB, Kansas City, Kansas.

The Importance of Avoiding Bacterial Contamination in Metabolic Studies. C. C. BELL, JR., DAVID M. HUME, and R. H. EGDAHL, Richmond.

The Effect of Caloric Equilibrium on Postoperative Utilization of Protein, Fat, and Carbohydrate. JOHN L. CAHILL, JOHN M. KINNEY, SHEILA H. NICHOLS, and LETA SUE BRANN, Boston.

Ascorbic Acid Metabolism in Surgical Patients. WILLIAM W. COON, Ann Arbor.

Alteration of Electrophoretic Patterns in Thymectomized Dogs. H. EDWARD GARRETT and GEORGE L. JORDAN, JR., Houston.

Bile-Renal Fistulas and Cholesterol Metabolism in Dogs; New Techniques and Findings. ANDRES GABEL, GEORGE COX, MARTHA ZABOR, and STEVEN G. ECONOMOU, Chicago.

Bile Pigment Metabolism Studies by Choledochocaval Anastomosis. C. THOMAS FITTS and WILLIAM A. NEELY, Jackson.

Thoracic Duct Lymph Studies in Oliguric Patients. ERNEST S. BREED and ALLAN E. DUMONT, New York.

Blood Volume Studies in Pediatric Surgical Patients. WILLIAM R. RICHARDSON, Oklahoma City.

Facilitation of Blood Volume Measurements. JOHN A. WILLIAMS, JAMES B. WILLIAMS, and JACOB FINE, Boston.

**Tuesday, 8:30 a.m.—12:00 noon**

CARDIO-ANGIOLOGY

Glucose Protection of the Canine Kidney Against Urokon Injury During Abdominal Aortography. EDWARD M. LANCE and DUNCAN A. KILLEN, Nashville.

The Protective Action of Low Molecular Weight Dextran upon Intravenous Hypaque Toxicity. EUGENE F. BERNSTEIN and ROBERT L. EVANS, Minneapolis.

Continuous Recording of Blood Oxygen Content. LELAND C. CLARK, JR., Birmingham.

Exploration into the Possibilities of Venous Inflow Occlusion During Angiocardiography. JOHN K. STEVENSON, MELVIN M. FIGLEY, and LEON A. PHILLIPS, Seattle.

Ascorbic Acid Dilution Curves in Cardiovascular Diagnosis. WILLIAM W. PFAFF, PETER FROMMER, and ANDREW G. MORROW, Bethesda.

Assessment of a Dye Technique for Measuring Graded Mitral Regurgitation in Dogs. DAVID E. DONALD, CHARLES P. NEWCOMBE, JOHN D. SINCLAIR, and EARL H. WOOD, Rochester, Minnesota.

Comparison of the Platinum-Rhodium-Hydrogen Electrode, Dye-Dilution, and Oxygen Methods in Detecting Shunts. ALBERT L. HYMAN, EDWARD S. HYMAN, ANTONIO QUIROZ, and JAMES GANTT, New Orleans.

Relationship of Spinal Fluid Pressure and Incidence of Paraplegia Following Temporary Aortic Occlusion; an Experimental Study. F. WILLIAM BLAISDELL and DENTON A. COOLEY, Houston.

Aeroembolus; a Protective Substance. WILLIAM G. MALETTE, JOHN P. FITZGERALD, and BEN EISEMAN, Denver.

Studies of Coronary Artery Distribution in Congenital Heart Disease. KEITH REEMTSMA and CHARLES G. LONGENECKER, New Orleans.

Influence of Metabolic Acidosis on Pressor Responses to Epinephrine in Intact Versus Cardiac Bypass Dogs. DAVID D. SNYDER, HOWARD B. KEITH, and GILBERT S. CAMPBELL, Oklahoma City.

Effects of Several Sympathomimetic Amines (Levarterenol, Phenylephrine, and Epinephrine) on Coronary Blood Flow During Cardiopulmonary Bypass. E. E. ALDINGER, WENDELL B. THROWER, and T. D. DARBY, Charleston.

**Tuesday, 8:30 a.m.—12:00 noon**

PLASTIC SURGERY

An Evaluation of Tissue Changes in the Healing Wound by Fluorescent Staining. JOSEPH C. DARIN, WILBERT WIVIOTT, RUSSELL MAYNARD, and WILLIAM H. FRACKELTON, Milwaukee.

Experimental Tendon Suture to Bone. ALAN D. FORWARD and R. J. COWAN, Vancouver.

The Effect of Some Rate Regulating Substances on the Synthesis of Collagen in Healing Wounds. ERLE E. PEACOCK, JR., Chapel Hill.

Leucocytic Patterns in Patients with Granulating Burns. J. E. BENNETT, E. W. HOUSTON, J. A. BASS, and TRUMAN G. BLOCKER, JR., Galveston.

Accelerated Excision and Grafting in the Lethal Burn. LESTER M. CRAMER, DANIEL B. CARROLL, and ROBERT M. MCCORMACK, Rochester, New York.

Rotation of Esophageal and Pharyngeal Flaps for Reconstruction of the Cervical Esophagus. FRANK C. MARCHETTA, KUMAO SAKO, and PATRICK J. CREEDON, Buffalo.

Studies on the Cellular Characteristics and Antibody Production of Lymphatic Tissue Homografts Surviving in Diffusion Chambers. DAVID C. MARSHALL, NANCY S. CROWELL, and SOMERS H. STURGIS, Boston.

6-Mercaptopurine and the Homograft Reaction. CHARLES A. HUBAY, ARNOLD POWELL, and WILLIAM D. HOLDEN, Cleveland.

The Prolongation of Functional Survival of Canine Renal Homografts by 6-Mercaptopurine. C. F. ZUKOSKI, H. M. LEE, and DAVID M. HUME, Richmond.

Graft-Host Interactions After Kidney Slices Transplantation in Inbred Mice. H. BROWNELL WHEELER and JOSEPH M. CORSON, Boston.

A Study of the Metabolic Response to Surgery in Paraplegics. HARVEY KRIEGER, STANLEY LEVEY, WILLIAM R. DRUCKER, and WILLIAM E. ABBOTT, Cleveland.

The Maintenance of Skin in Tissue Culture as an Intact Organ. DICRAN GOULIAN, RONALD GILLETTE, and ANGELICA FINDLEY, New York.

**Tuesday, 1:30—5:00 p.m.**

GASTRIC PHYSIOLOGY

The Use of Ion Exchange Resin in the Protection of Skin Against the Action of Digestive Juice. GEORGE S. RICHARDSON and ROBERT H. PURDY, Boston.

The Vascular Component in the Causal Genesis of Peptic Ulcer. REZA SEIRAFI, VILMA JANSONS, EVALDO RUIZ, and L. CORSAN REID, New York.

Fluid Balance in Pancreatic-Induced Peptic Ulceration. DAN W. ELLIOTT, EDWARD PASSARO, and WILLIAM S. ELLIOTT, Columbus, Ohio.

Studies on the Relationship of Antral and Fundic Denervation to Gastric Secretion. ALSTRUP N. JOHNSON, JR., LESTER R. DRAGSTEDT II, E. RICHARD SINGER, and HARRY A. OBERHELMAN, JR., Chicago.

The Effect of Vagotomy on the Intestinal Phase of Gastric Secretion. LESTER R. DRAGSTEDT II, ALSTRUP N. JOHNSON, JR., E. RICHARD SINGER, and HARRY A. OBERHELMAN, JR., Chicago.

Quantitative Acid Secretory Studies in Monkey Isolated Gastric Pouches During Hypoglycemic Stress. CLOYDE L. FAUSNAUGH, LLOYD M. NYHUS, and HENRY N. HARKINS, Seattle.

Gastric Secretion of ABO Blood Group Antigens. JOSEPH A. BUCKWALTER and GEORGE B. JERZY GLASS, Iowa City.

A New Method of Studying "Acid Inhibition" and "Acid Rebound" in Dogs. PETER SHROCK, DANIEL SHAPIRA, and DAVID STATE, New York.

Effect of 48/80 on Plasma Pepsinogen. KONSTANTY KOWALEWSKI, Edmonton.

Role of Residue Stomach in Hypersecretion of Heidenhain Pouch After Portacaval Transposition. WARD D. O'SULLIVAN, M. L. CANTLIN, R. D. SWEENEY, and H. M. ROSTEING, Philadelphia.

Antral Hyperfunction Following Portacaval Shunt. ALDO CASTANEDA, Minneapolis.

Further Studies on the Mechanism of Gastric Hypersecretion After Portacaval Shunts. P. G. CORNISH, W. SILEN, BEN EISEMAN, and L. P. WOODS, Denver.

**Tuesday, 1:30—5:00 p.m.**

## EXTRACORPOREAL CIRCULATION

Experimental Partial Perfusion. ROBERT B. RUTHERFORD and HENRY SWAN, Denver.

The Relationship of Coronary Blood Flow to the Effectiveness of Mechanical Support of the Circulation in Acute Heart Failure. EDGAR A. STORLI, JOHN E. CONNOLLY, MARVIN B. BAGANER, and DAVID L. BRUNS, Palo Alto.

Cardiac Bypass with the Pump-Oxygenator for Circulatory Support During Cardiac Decompensation. A. N. GEREIN, R. D. JONES, and FREDERICK S. CROSS, Cleveland.

Prolonged Venovenous Perfusion with Oxygenation; Experimental Hypoxia of Respiratory Origin. IRWIN KRASNA, LEONARD STEINFELD, ISADORE KREEL, FRED HORWITZ, and IVAN D. BARANOFSKY, New York.

Prosthesis for Pulmonary Artery Bypass in Severe Tetralogy of Fallot. MARIANO LOPEZ-BELIO, GEORGE TASAKI, FERNANDO GOMEZ, LUIS SANCHEZ, and ORMAND C. JULIAN, Chicago.

Cardiac Output Studies in Dogs with Normal Right Ventricle and Enlarged Right Ventricular Outflow Tract with Pulmonary Insufficiency. RICHARD W. ERNST, YOUNG KYOON LEE, and C. WALTON LILLEHEI, Minneapolis.

Renal Circulatory Response to Cardiopulmonary Bypass. ROBERT L. REPLOGLE and ROBERT E. GROSS, Boston.

A Study of the Physiological Changes in the Lungs During Cardiopulmonary Bypass. ROBERT S. CARTWRIGHT, THOMAS P. K. LIM, and ULRICH C. LUFT, Albuquerque.

The Effect of Extracorporeal Circulation upon Portal Hemodynamics. JAY L. ANKENEY and PETER H. VILES, Cleveland.

The Use of Stored Acid-Citrate-Dextrose (ACD) Blood for Clinical Extracorporeal Circulation. ANDREW V. FOOTE, MICHAEL TREDE, and JAMES V. MALONEY, JR., Los Angeles.

An Efficient, Low-Volume, Semidisposable Screen Oxygenator. BENSON B. ROE, W. L. WEIRICH, D. MOORE, and B. SWENSON, San Francisco.

A New Pump-Oxygenator. ERNEST M. BARSAMIAN, STANLEY W. JACOB, and SAMUEL C. COLLINS, Boston.

**Wednesday, 8:30 a.m.—12:00 noon**

## PHYSIOLOGY OF THE ESOPHAGUS, STOMACH, AND SMALL BOWEL

The Role of Cortisone in the Production of Peptic Esophagitis in the Cat. JEANNE BUTTERFIELD, JAMES G. BASSETT, and DONALD R. COOPER, Philadelphia.

Changes in the Motor Action of the Esophagus and the Gastroesophageal Sphincter After Vagotomy in Dogs. STEPHEN W. CARVETH, JERRY F. SCHLEGEL, CHARLES F. CODE, and F. HENRY ELLIS, JR., Rochester, Minnesota.

A New Technique Utilizing a Phrenically Innervated Diaphragmatic Segment as a Substitute Lower Esophageal "Intrinsic" Sphincter. PHYLLIS R. INGRAM and WILLIAM H. MULLER, JR., Charlottesville.

Blood Flow Studies in the Experimental Dumping Syndrome. WILFRED M. HUSE and DAVID B. HINSHAW, Los Angeles.

Evaluation of Autonomic Nervous System Response in Patients with the Dumping Syndrome. R. B. HICKLER, JOHN R. BROOKS, J. T. HAMLIN III, and R. G. HOSKINS, Boston.

Regulation of Gastric Emptying by Gastroduodenal Interposition of the Ileocecal Sphincter Following Ablation of the Pylorus. PANAGIOTIS N. SYMBAS, D. A. KILLEN, and H. WILLIAM SCOTT, JR., Nashville.

Studies of Fat Digestion in Patients After Antral Resection and Vagotomy; Comparison of the Effects of Gastroduodenal and Gastrojejunal Anastomoses. F. BEACHLEY MAIN, H. WILLIAM SCOTT, JR., and Walter G. GOBBEL, JR., Nashville.

Detection of the Site of Bleeding from the Upper Alimentary Canal by the Use of Radioactive Chromium. IRVING M. ARIEL, New York.

An Experimental Method of Localizing Gastrointestinal Hemorrhage. WILLIAM V. HEALEY, ROBERT RIGGINS, RICHARD WHITE, DAVID V. HABIF, and WILLINGTON B. STEWART, New York.

Double-Blind Study of the Effect of D-Pantothenyl Alcohol on Experimental Postoperative Ileus. MICHAEL A. POLACEK, A. STEPHEN CLOSE, and EDWIN H. ELLISON, Milwaukee.

Decompressive Enterotomy, Effect on Fluid Losses in Distal Small Bowel Obstruction. WILLIAM T. REDFERN, A. STEPHEN CLOSE, and EDWIN H. ELLISON, Milwaukee.

**Wednesday, 8:30 a.m.—12:00 noon**

CARDIO-ANGIOLOGY

The Radiation Plethysmograph; a New Technique for Evaluating Circulation in Human Extremities. RICHARD W. STEENBURG and BJORN THOMASSON, Baltimore.

The Development and Regression of Collateral Circulation. CHARLES G. LONGENECKER, KEITH REEMTSMA, and OSCAR CREECH, JR., New Orleans.

The Effect of Anoxia on Ion Transport Across Blood Vessel Walls. P. N. SAWYER, I. VALMONT, H. STEINBAUM, J. LEVINE, and R. MAZLIN, Brooklyn.

Lymphangiography Via Subcutaneous Injection. C. DANESE, Philadelphia.

Obliteration of Congenital Arteriovenous Fistulae by Embolization with Microspheres. JOHN J. MCCAUGHAN, JR., Memphis.

The Atherosclerosis of Aortic and Pulmonary Artery Exchange Autografts. WILLIAM C. WOYDA, ERNEST M. BERKAS, and DONALD J. FERGUSON, Minneapolis.

The Effect of Hypertension on Experimental Atherosclerosis. YOSHIO SAKO, Minneapolis.

The Rapid Production of Experimental Atherogenesis. SAM E. STEPHENSON, JR., RACHEL YOUNGER, and ANTHONY J. MUNOZ, Nashville.

Thrombosis—Factors Influencing the Prevention and Treatment of Thrombosis. HUGO L. DEATON, WILLIAM G. ANLYAN, and LYNN FORT III, Durham.

Chemical Correction of Citrated Bank Blood by Means of a Parallel Flow Blood Dialyzer. SIDNEY ANTHONE, ROLAND ANTHONE, and JOSE A. RODRIGUEZ, Buffalo.

Mechanisms of Hypoxia in Left to Right Shunts. LOIS T. ELLISON, DAVID P. HALL, and ROBERT G. ELLISON, Augusta.

Snakebite; Treatment by Isolation Perfusion Technique. JAMES BORDEN, ERIC W. FONKALSRUD, VICTOR NEWCOMER, WILLIAM P. LONGMIRE, JR., and DONALD B. ROCHLIN, Los Angeles.

**Wednesday, 8:30 a.m.—12:00 noon**

BURNS, WOUND HEALING, AND INFECTION

Early Differentiation of Full Thickness Burns. THOMAS C. KING and P. B. PRICE, Salt Lake City.

A Simple, Accurate Method for Early Differentiation of Partial and Full Thickness Burns. J. HAROLD CONN, W. R. FAIN, and ELIZABETH FERRINGTON, Jackson.

The Immune System in Thermal Injury; Burned Skin as a Source of Antigenic Substances. JOSEPH F. ALBRIGHT and E. R. BERRY, Richmond.

Zinc Studies in Skin Repair. WILLIAM H. STRAIN, WALTER J. PORIES, and J. RAYMOND HINSHAW, Rochester, New York.

The Effect of Bacterial Endotoxin on Connective Tissue Growth and Wound Tensile Strength. U. FREIHOFFER, E. A. ROBINSON, D. S. JACKSON, and J. ENGLEBERT DUNPHY, Portland.

Collagen Structure and Metabolism. HYMAN ROSEN, ALEXANDER KESSLER, and STANLEY M. LEVENSON, Washington.

Wound Healing in Experimental Diabetes. RICHARD ROSEN and IRVING F. ENQUIST, Brooklyn.

Prophylactic Penicillin Administration in Experimental Wound Infections. J. W. ALEXANDER, JOHN J. MCGLOIN, and WILLIAM A. ALTEMEIER, Cincinnati.

A New Method for the Determination of Staphylococcal Antibody Titers. L. R. RUDOLF and R. H. LEWIS, Boston.

Factors Influencing the Treatment of Staphylococcal Infections by Bacteriophage. W. MUIR, T. B. YOUNG, and WILLIAM S. BLAKEMORE, Philadelphia.

Antibiotics in Experimental Bile Peritonitis. JAMES S. SHELBY, ALVIN COTLAR, FRANKLIN MASSARI, MOHAMMAD ATIK, and ISIDORE COHN, JR., New Orleans.

A Disposable Plastic Isolator for Operating in a Sterile Environment. STANLEY M. LEVENSON, OLE J. MALM, RICHARD E. HOROWITZ, WILLIAM H. MONCRIEF, JR., Washington, D. C., and P. C. TREXLER, South Bend.

**Wednesday, 1:30—5:00 p.m.**

PHYSIOLOGY OF THE LIVER AND PANCREAS

Hemodynamic Effects of Posterior Pituitrin in Cirrhosis. JULIUS J. BABER, M. CHAFIZADEH, EARL J. HALLIGAN, and CARROLL M. LEEVY, Jersey City.

Plasma Protein Synthesis in the Normal Dog and After Total Hepatectomy. JOHN C. KUKRAL, JACK D. KERTH, DAVID W. CROMER, and JOSEPH SPORN, Chicago.

Effect of Hepatic Congestion on Bile Excretion. HARRY G. LIGHT, Philadelphia.

Effect of the Molecular Size of Dextran on Liver and Kidney Oxygen Tension. J. RAYMOND HINSHAW, W. J. PORIES, PAUL D. HARRIS, T. P. DAVIS, and SEYMOUR I. SCHWARTZ, Rochester, New York.

Polarographic Evaluation of the Effect of Pitressin on Hepatic Oxygen Tension. PAUL D. HARRIS and SEYMOUR I. SCHWARTZ, Rochester, New York.

The Influence of Intragastric Cooling on Acute Experimental Pancreatitis. DONALD C. NABSETH, ALFRED J. NICHOLSON, WILLIAM H. NEWMAN, LAWRENCE TOSE, and ARNOLD E. REIF, Boston.

The Effect of Alcohol on Pancreatic Secretion. BRUCE WALTON, HERBERT SCHAPIRO, and EDWARD R. WOODWARD, Gainesville.

The Occurrence of Pancreatic Antibodies and the Nature of the Pancreatic Antigen. ALAN THAL, Minneapolis.

Dietary Factors Leading to Chronic Pancreatitis. N. T. MCPHEDRAN and COLIN C. LUCAS, Toronto.

The Effect of Intraduodenal Hypertonic Glucose on Biliary and Pancreatic Secretion. JOHN J. KNIGHTLY, PARKER VANAMEE, and WALTER LAWRENCE, JR., New York.

Pancreatitis with Hyperlipemia. EDWARD W. EHRLICH, S. SPITZER, and JOHN M. HOWARD, Philadelphia.

Studies on the Origin of Normal Blood Amylase. THOMAS V. CRAIG, Columbus, Ohio.

**Wednesday, 1:30—5:00 p.m.**

CARDIOVASCULAR TECHNIQUE

Double Coronary Artery—Internal Mammary Artery Anastomoses, Tantalum Ring Technique. MICHAEL ROHMAN, ROBERT H. GOETZ, and RONALD DEE, New York.

Experimental Studies in Small Blood Vessel Surgery—IV, Nonsuture Anastomosis of Arteries and Veins Using Flanged Ring Prostheses and Plastic Adhesive. CHARLES A. CARTON, LAIBE A. KESSLER, BERNARD SEIDENBERG, and ELLIOTT S. HURWITT, New York.

Modified Nonsuture Anastomosis of Coronary Artery and Internal Mammary Artery. RAM S. RATAN, MARIO LEON, JOHN B. LOVETTE, BERNARD LEVOWITZ, GEORGE J. MAGOVERN, and EDWARD M. KENT, Pittsburgh.

A New Technique for Small Artery End-to-End Anastomosis. GORDON P. HOLT and F. JOHN LEWIS, Chicago.

Microsurgery in Small Vessel Anastomosis. JULIUS H. JACOBSON II and ERNESTO L. SUAREZ, Burlington, Vermont.

Coronary Artery Surgery in Dogs with Venoveno Cooling and Acetylcholine Arrest. GEORGE R. DAICOFF, JOSEPH R. LANCASTER, PAUL B. STEWART, NORMAN J. SIDERIUS, and PETER V. MOULDER, Chicago.

Prolonged Electrical Stimulation of the Heart. A. L. TOOLE, E. LONGO, A. MAURO, and WILLIAM W. L. GLENN, New Haven.

The Development of an Epicardial-Endocardial Electrode for Permanent Placement in Stokes-Adams Disease. VINCENT L. GOTT and ROBERT SELLERS, Minneapolis.

Clinical Experimental Application of a New Treatment for Cardiac Arrest. JAMES R. JUDE, W. B. KOUWENHOVEN, and G. G. KNICKERBOCKER, Baltimore.

Evaluation of the Dammann-Muller Procedure for Large Left-to-Right Shunts in Infancy. RODNEY T. SMITH and JAMES A. MCEACHEN, Santa Monica.

Mitral Valve Replacement. HECTOR S. HOWARD, V. L. WILLMAN, and C. ROLLINS HANLON, St. Louis.

Total Mitral Valve Replacement: Fixation and Thrombosis. ALBERT STARR, Portland.

**Wednesday, 1:30—5:00 p.m.**

OBSTETRICS AND GYNECOLOGY

Interruption of Uterine Blood Flow; a New Technique for the Production of Congenital Malformations; Comparison of the Eighth, Ninth, and Tenth Days of Gestation. JOHN B. FRANKLIN and ROBERT L. BRENT, Philadelphia.

A Transistorized Fetal Heart Monitor. EDWARD H. HON, New Haven.

Placental Homotransplantation Using the Millipore Chamber in the Rat. TA-JUNG LIN, Cleveland.

Effects of Maternally Administered Drugs on the Fetus in Utero. B. T. JACKSON, G. J. PIASECKI, and R. H. EGDAHL, Richmond.

Host-Homograft Interactions Following Leucocytic Transfusion During Pregnancy. RICHARD H. ANDRESEN, G. M. HASS, D. A. MADDEN, and S. PAPADOPOULOS, Chicago.

The Role of the Mind in the Genesis of Toxemia of Pregnancy. C. A. DOUGLAS RINGROSE, Edmonton.

Germfree Guinea Pig Delivery by Hysterectomy. JEROME J. LANDY, THEODORE G. YERASIMIDES, JAMES H. GROWDON, and SYDNEY C. BAUSOR, Little Rock.

Intrauterine Fetal Hypophysectomy in Primates; a Technique. DONALD L. HUTCHINSON, WILLIAM H. HINDLE, and J. L. WESTOVER, Los Angeles.

A Technique for Reconstruction of Fallopian Tube; a Preliminary Report. A. G. CHARLES, J. E. LABES, M. R. COHEN, and W. C. SHOEMAKER, Chicago.

The Role of the Uterine Isthmus in Cervical Incompetence. EDWARD C. MANN, New York.

Pelvic Perfusion—I, the Feasibility of Isolation of the Vascular Compartment of the Canine Pelvis. GEORGE R. PROUT, JR., NORMAN KENYON, W. GLEN MOSS, and DANIEL S. MARTIN, Miami.

Thrombectomy for Acute Iliofemoral Venous Thrombosis. J. ALEX HALLER, JR., Louisville.

**Thursday, 8:30 a.m.—12:00 noon**

## CARDIO-ANGIOLOGY AND PORTAL HYPERTENSION

Effect of Intermittent Cardiac Ischemia on Myocardial Oxygen Availability and Left Ventricular Function. JACK J. GREENBERG and HENRY EDMUNDS, JR., Bethesda.

Chronic Extrinsic Cardiac Denervation; Physiologic and Pharmacologic Studies Following Regional Neural Ablation. J. W. GILBERT, T. COOPER, R. D. BLOODWELL, L. J. GREENFIELD, N. P. COLLINS, and R. J. CROUT, Bethesda.

Bacterial Contamination of Oxygen Using Cardiopulmonary Bypassing—Importance and One Method of Control. J. D. MORTENSEN, SCOTT M. SMITH, and GILBERT HILL, Salt Lake City.

Collateral Pulmonary Blood Flow After Ligation of the Left Main Pulmonary Artery. ROBERT H. GOETZ, MICHAEL ROHMAN, RONALD DEE, JORDAN D. HALLER, and DAVID STATE, New York.

The Effects of Ultrasound on Normal and Calcific Cardiac Valves. ALEXANDER C. HERING, H. PHILLIP HOVNANIAN, ROBERT W. OLWINE, TIMOTHY BRENNAN, and ELTON WATKINS, JR., Boston.

Electrocardiographic Response to Experimental Coarctation of the Aorta in the Fetus in Utero. B. T. JACKSON, G. J. PIASECKI, and R. H. EGDAHL, Richmond.

Enteric Arteriovenous Anastomoses and Their Contribution to Portal Hemodynamics. LEROY L. JOHNSON, HARRY M. NELSON, WILLIAM H. HARDESTY, and GERALD W. PESKIN, Philadelphia.

Autonomic Influences on Portal Pressure. A. F. PETERS, ROBERT GRANGER, and S. R. POWERS, JR., Albany.

Reduction of Portal Hypertension by Nonshunting Methods in Cirrhotics. JOHN J. CINCOTTI, HAROLD F. WELCH, JOHN H. CARTER, JAMES H. CLEARY, ANTONIO BOBA, and JOHN A. NELSON, Albany.

An Evaluation of the Side-to-Side Portacaval Shunt. DONALD G. MULDER and JOHN F. MURRAY, Los Angeles.

The Effect of Side-to-Side Portacaval Shunt on Experimentally Produced Ascites in Dogs. EDWARD J. MARGULIES and C. STUART WELCH, Albany.

Relation Between Hepatic Blood Flow and Function in Normal and Cirrhotic Dogs After Portacaval Shunt or Transposition. F. W. HEER, D. E. SILVIUS, and HAROLD A. HARPER, San Francisco.

**Thursday, 8:30 a.m.—12:00 noon**

## ETIOLOGY AND TREATMENT OF SHOCK

Hemorrhagic Shock in Dogs Treated with Extracorporeal Circulation; a Study of Survival Time and Blood Chemistries. R. ADAMS COWLEY, ANDREAS DEMETRIADES, ARLIE R. MANSBERGER, JR., SAFOUH ATTAR, WILLIAM G. ESMOND, and SAMUEL P. BESSMAN, Baltimore.

Glycogen Metabolism During Hemorrhagic Shock in the Rat. JOSEPH G. STRAWITZ and HELEN HIFT, Buffalo.

Distributional Changes in Extracellular Fluid During Acute Hemorrhagic Shock. GEORGE T. SHIRES, FRANK T. BROWN, PETE C. CANIZARO, and NANCY SOMERVILLE, Dallas.

A Comparison of Intestinal Tissue Blood Flow in Experimental Shock Due to Hemorrhage, Endotoxin, and Adrenalin; and in Endotoxin Shock Pretreated with Hydrocortisone or Dibenzylene. RALPH R. RAYNER, LLOYD D. MACLEAN, and EUGENE GRIM, St. Paul.

Studies on the Hepatic and Visceral Microcirculation During Shock and After Epinephrine Administration; a Preliminary Report. N. R. BRILL and W. C. SHOEMAKER, Chicago.

The Effect of Norepinephrine and Blood Transfusion on Urine Flow Following Arterial Hemorrhage in Dogs. J. H. WULSIN and WILLIAM A. ALTEMEIER, Cincinnati.

Influence of Increments of a Vasopressor on the Rate of Urine Formation in Graded Hemorrhage. JERALD JACKSON and WATTS R. WEBB, Jackson.

Action of Noradrenalin and Ascorbate on Hydroxylation of Progesterone by Bovine Adrenocortical Homogenates. David Y. Cooper, Otto Rosenthal, and William S. Blakemore, Philadelphia.

Studies of Extracellular Volume in the Regulation of Antidiuretic Hormone. Theodor B. Grage, Joan Winter, and Bernard Zimmermann, Minneapolis.

The Effect of the Acute Administration of Corticosteroids on the Adrenocortical Response to Surgery. John L. Myers, Edward T. O'Hara, John W. Heizer, Harvey Liberman, and Leon J. Marks, Boston.

Endocrine Control of Plasma Lipids. Edward Paloyan, Paul Vincent Harper, Jr., and Hannah B. Watkins, Chicago.

The Influence of Hypothermia on Metabolism During Hemorrhagic Shock. William R. Drucker, Cleveland.

**Thursday, 8:30 a.m.—12:00 noon**

NEUROLOGIC SURGERY

The Effect of Hypotensive Drugs and Hypophysectomy upon the Adrenal Cortex of Dogs. Eckhard Fischer, Ruben Brochner, Arthur S. Biddle, and Loyal Davis, Chicago.

Effects of Certain Subcortical Brain Lesions on Induced Tremor in the Cat. R. H. Strassburger and Lyle A. French, Minneapolis.

Effects of Multiple Thalamic and/or Pallidal Lesions in Extrapyramidal Diseases. Blain S. Nashold, Jr. and Anna D. Ottolenghi, Durham.

Total Hemispherectomy in the Cat. Joseph E. Bogen and Berry Campbell, Los Angeles.

The Role of Limbic Structures in Learned Behavior. Orlando J. Andy and J. Mitchell, Jackson.

Differential Production of Vascular Changes and Temporarily Sustained Hypertension in Cats and Dogs. J. F. Kell, Jr., H. G. Langford, E. C. Hoff, and G. R. Henningar, Richmond.

Altered Activity at the Margins of Human Epileptogenic Foci. Sidney Goldring, Michael J. Jerva, Thomas G. Holmes, and James L. O'Leary, St. Louis.

The Fate and Distribution of Hypertonic Urea Solutions; a Preliminary Report. David Gilboe, Manucher Javid, and Paul Frechette, Madison.

The Influence of Intravenous Solutions on Cerebrospinal Fluid Pressure. Eugene B. Elam, John W. Devanney, and Robert L. McLaurin, Cincinnati.

Percutaneous Retrograde Cerebral Sinography. Louis L. Battey and George W. Smith, Augusta.

Intraosseous Epidural Venography in the Diagnosis of Surgical Diseases of the Lumbar Spine. Erich G. Krueger and Robert Schobinger, New York.

Relationship of the Spinothalamic Tract Fibers to the Dentate Ligament in the Thoracic and the Cervical Cord. Dogan M. Perese, Buffalo.

**Thursday, 8:30 a.m.—12:00 noon**

UROLOGY

Regional Perfusion of the Prostatic Circulation. A. M. Behnam and C. V. Hodges, Portland.

Experimental and Clinical Study of Operations for Urinary Incontinence. Willard E. Goodwin and Abraham Cockett, Los Angeles.

Ureteral Response to Elevated Intravesical Pressure in Humans. James M. Pierce, Jr., and Esmond Braun, Detroit.

Intravesical Pressure Changes During Endoscopic Procedures and Their Clinical Significance. Harry W. Schoenberg and John J. Murphy, Philadelphia.

The Causation of Postoperative Contracture of the Vesical Neck. John C. Campbell and Laurence F. Greene, Rochester, Minnesota.

A New Method of Ureteroneocystostomy. Nicholas F. Viek and Richard Uhlman, Philadelphia.

Experimental Pyelonephritis, Part I. William H. Rattner and Esmond Braun, Detroit.

Early Differential Diagnosis of Postoperative Anuria Using the Radioisotope Renogram. Joseph J. Libretti, Vincent J. O'Conor, Jr., and John T. Grayhack, Chicago.

The Treatment of Acute Hyperkalemia Utilizing a "Resin Artificial Kidney." Robert J. Moore and Theodore H. Lehman, Portland.

Experimental Revascularization of the Kidney. James F. Glenn, B. Marvin Harvard, and Clyde L. Deming, New Haven.

Further Experiences with Intermittent Occlusion of the Renal Pedicle. Allan Yoho, Paul J. Stueber, Jr., Simon Koletsky, and Lester Persky, Cleveland.

The Influence of Infrarenal Aortic Cross-Clamping on Renal Blood Flow. N. O. Chamberlin, P. N. Symbas, J. H. Foster, and A. P. Harris, Nashville.

**Thursday, 1:30 p.m.—3:00 p.m.**

NEUROLOGIC SURGERY

Possible Radiation Therapy of Cephalic Neoplasms by Perfusion of Short-Lived Isotopes; Use of Zinc-69. ROBERT G. OJEMANN and GORDON L. BROWNELL, Boston.

Experimental Studies in Small Blood Vessel Surgery Using Plastic Adhesive—III, Prevention of Aneurysmal Dilatation. LAIBE A. KESSLER and CHARLES A. CARTON, New York.

An Experimental Study of the Technique and Effects of Selective Brain Cooling. JOHN E. CONNOLLY, EDMUND J. HARRIS, DAVID L. BRUNS, JOHN W. SMITH, and ROBERT BOYD, Palo Alto.

Cardiovascular Effects of Local Brain Stem Cooling. NORMAN CHATER and JOHN E. ADAMS, San Francisco.

Total Cerebral Ischemia and Perfusion Hypothermia in the Dog. ROBERT J. WHITE, DAVID E. DONALD, and DAVID FERGUSON, Rochester, Minnesota.

Profound Hypothermia by Extracorporeal Cooling. CHARLES A. BUCKNAM and ANIBAL GALINDO, Bethesda.

## *Motion Picture Program*

**Monday, 8:30 a.m.—12:00 noon**

WILLIAM E. ADAMS, Chicago, *Presiding.*

Surgical Repair of Dupuytren's Contracture. STUART D. GORDON, Toronto.

Undescended Testis. ROBERT J. PRENTISS, San Diego.

Surgical Repair of Ligaments of the Ankle Following Acute Injuries. LESLIE M. BODNAR and JOSEPH B. CROWLEY, South Bend.

Correction of Pectus Carinatum (Pigeon Breast). MARK M. RAVITCH, Baltimore.

Esophagoplasty and Colon Interposition for Stenosis. HUGH B. LYNN, Louisville.

Benign Neoplasm of the Papilla of Vater. WILLIAM H. REMINE, Rochester, Minnesota.

Cases of Carcinoid Syndrome with Special Reference to Primary Gastric Carcinoid. C. FREDERICK KITTLE, ARTHUR P. KLOTZ, JOHN B. CHRISTODOULOPOULOS, and E. G. DIMOND, Kansas City, Kansas.

A New Method for the Study of Bronchovascular Anatomy. WILSON WEISEL, GEORGE F. FLYNN, WILLIAM GORMAN, and DERWARD LEPLEY, JR., Milwaukee.

Anomalous Pulmonary Vein to the Inferior Vena Cava. C. FREDERICK KITTLE, Kansas City, Kansas.

**Tuesday, 1:00—5:00 p.m.**

CHARLES B. PUESTOW, Chicago, *Presiding.*

The Surgical Anatomy of Pulmonary Hilum—I, Right Lung. EDWARD A. BOYDEN and FRANKLIN R. SMITH, Seattle.

Mesenteric Cysts. JAMES D. HARDY and JAMES C. GRIFFEN, Jackson.

Unguided Missiles—Power Mower Injuries. WATTS R. WEBB, Jackson.

Achalasia of Esophagus. F. HENRY ELLIS, JR., and ARTHUR M. OLSEN, Rochester, Minnesota.

Vagotomy, Pyloroplasty, and Tube Gastrostomy. STANLEY O. HOERR, Cleveland.

Cholecystectomy and Combined Supra and Transduodenal Exploration of the Common Duct. HOWARD MAHORNER, New Orleans.

Repair of the Injured Common Duct. RICHARD B. CATTELL, Boston.

Discussion, Question, and Answer Period.

Premiere showing of: Technique of Dressing Wounds to Prevent Cross Infection. Technical Advisor: CARL W. WALTER, Boston.

**Wednesday, 1:00—5:00 p.m.**

EDWARD S. JUDD, Rochester, *Presiding.*

"Hands We Trust." A motion picture describing the education of a surgeon.

Inferior Vena Cava Ligation with Thrombectomy. JOHN BLALOCK, New Orleans.

Femoral Hernia. CLARENCE DENNIS, Brooklyn.

Inguinal Hernioplasty. CHESTER B. MCVAY, Yankton, South Dakota.

Cholecystectomy for Acute Cholecystitis. DEWARD O. FERRIS, Rochester, Minnesota.

Abdominal Angina; Surgical Treatment with Bypass Graft from Abdominal Aorta to Celiac and Superior Mesenteric Arteries. GEORGE C. MORRIS, JR. and MICHAEL E. DEBAKEY, Houston.

Color Changes in Skin Lesions. KENNETH C. OLSON, Buffalo.

Radical Right Hemicolectomy with Segmental Duodenectomy and Aortocaval Node Dissection. JOHN L. MADDEN, New York.

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**Thursday, 1:00—3:30 p.m.**

PAUL V. HARPER, Chicago, *Presiding.*

Surgical Treatment of Renovascular Hypertension. GEORGE C. MORRIS, JR., MICHAEL E. DEBAKEY, E. STANLEY CRAWFORD, and DENTON A. COOLEY, Houston.

Kidney Transplant. DAVID M. HUME, Richmond.

Removal of Parathyroid Adenoma for Hyperparathyroidism. FRANCIS D. MOORE, Boston.

Hyperinsulinism, Islet Cell Adenoma of the Pancreas. HAROLD A. ZINTEL, New York.

Carcinoma of the Breast. CRANSTON W. HOLMAN, New York.

**Friday, 8:30 a.m.—12:00 noon**

FRANK L. GERBODE, San Francisco, *Presiding.*

Multiple Aneurysms: Case Presentations. ANDREW G. SHARF, Glendale.

Correction of Patent Ductus Arteriosus, Coarctation of Aorta, and Interventricular Septal Defect. ROBERT G. PONTIUS, Pittsburgh.

Excision of Aneurysm Due to Cystic Medial Necrosis of the Ascending Aorta. HENRY T. BAHNSON, Baltimore.

Side-to-Side Portacaval Shunt. JOHN L. MADDEN, New York.

Thoracoabdominal Approach for Excision of Large Abdominal Aortic Aneurysm. FREDERICK S. CROSS and ALFRED N. GEREIN, Cleveland.

Intrathoracic Aneurysm of the Vertebral Artery Associated with Coarctation of the Aorta. ELLIOTT S. HURWITT, New York.

Surgical Considerations in the Treatment of Cerebral Arterial Insufficiency. E. STANLEY CRAWFORD, MICHAEL E. DEBAKEY, GEORGE C. MORRIS, JR., and WILLIAM S. FIELDS, Houston.

Choice of Surgical Procedure in Aortoiliac Occlusive Disease. D. EMERICK SZILAGYI, ROGER F. SMITH, and JOHN G. WHITCOMB, Detroit.

Valvuloplasty for Mitral Stenosis. DWIGHT E. HARKEN, Boston.

**Friday, 1:00—5:00 p.m.**

THOMAS G. HAYS, Oakland, *Presiding.*

The Role of the Clavicle and Its Surgical Significance. LEROY C. ABBOTT and DONALD B. LUCAS, Los Angeles.

Laryngectomy; a Technique. KENNETH D. DEVINE, Rochester, Minnesota.

Diagnosis of Ventricular Septal Defects. JEROME H. KAY, SOL BERNSTEIN, and R. M. ANDERSON, Los Angeles.

Surgical Correction of Male Sterility. VINCENT J. O'CONOR, J. KENNETH SOKOL, and GEORGE J. BULKLEY, Chicago.

Patent Urachus. LAWRENCE S. MANN and GILBERT H. DEMANGE, Chicago.

Cold Knife Conization of the Uterine Cervix with Dilatation and Curettage. FREDERICK J. HOFMEISTER, Milwaukee.

Mouth to Mouth Rescue Breathing (Project 225-A). PETER SAFAR, Washington.

Thromboendarterectomy of the Left Common Carotid and Its Bifurcation. JOHN L. MADDEN, New York.

Disinfection of the Skin. CARL W. WALTER, Boston.

## *Television Program*

**Monday to Friday, mornings and afternoons**

Cardiac Surgery. FRANK GERBODE.

Radical Mastectomy. LEON GOLDMAN.

Correction of Undescended Testicle. EDWARD A. FREE.

Venous Shunt for Portal Hypertension. ROY B. COHN.

Bowel Resection. DONALD M. GALLAGHER.

Cholecystectomy. CARLTON MATHEWSON, JR.

Peripheral Arterial Surgery. EDWIN J. WYLIE.

Open Reduction of Fracture. C. HOWARD HATCHER.

Gastrectomy. HARRY A. OBERHELMAN, JR.

Hysterectomy. CHARLES E. MCLENNAN.

Pulmonary Resection. JOHN E. CONNOLLY.

Repair of Injured Hand. DONALD R. PRATT.

Radical Neck Dissection. FREDERICK P. SHIDLER.

Thyroidectomy. THOMAS S. NELSEN.